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PROCEEDINGS
of the
ROYAL SOCIETY OF MEDICINE

Published for
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by
H. K. LEWIS & Co. LTD., 136 GOWER STREET, LONDON, W.C.1
In U.S.A., GRUNE & STRATTON, INC., 381, FOURTH AVENUE, NEW YORK CITY
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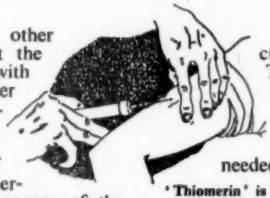

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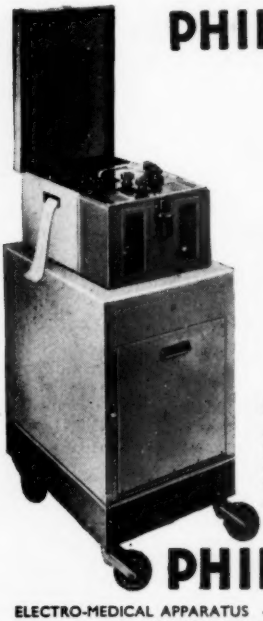

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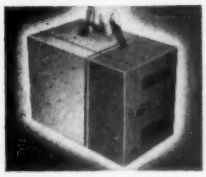

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Clinical Section

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[*December* 12, 1952]

Cushing's Syndrome in a Child of 2½ Years.—D. M. DAVIES, M.R.C.S., L.R.C.P. (by permission of J. BARRIE MURRAY, M.D., M.R.C.P., and F. N. GLOVER, M.S., F.R.C.S.).

Male, aged 2½ years. Normal at birth and developed normally (Fig. 1).

July 1952: Suddenly began to pass five or six soft yellow motions a day and seemed unusually sleepy. Ten days later, his face and abdomen became fatter, his appetite increased, and he began to wet the bed and to ask for drinks during the night; his motions became normal and he became less sleepy.

August 1952: At another hospital, he was found to weigh 35 lb. 4 oz. and to have slight albuminuria and an enlarged liver. A low carbohydrate diet had no effect on his obesity.

FIG. 1.—May 1952: Before the onset of the disease.

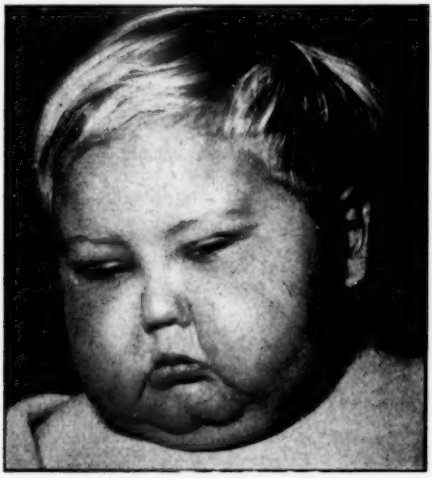

FIG. 2.—September 1952.
[Photograph: Mr. D. M. Thomas.]

September 5, 1952: A pad of fat appeared over the lower cervical spine and several raised spots appeared on both cheeks. His behaviour changed; he began to bite his nails, seemed sleepy all the time and refused to speak to anyone except his mother. Three days later he was admitted to the Bolingbroke Hospital.

Past history.—Birth weight 7 lb. 6 oz. No previous illnesses.

Family history.—Mother and father well. Twin brothers, aged 3½ years, well.

On examination.—Sleepy child with marked obesity of face, neck, and trunk (Fig. 2). Fatty pad over lower cervical spine. Acne of both cheeks. Fine downy hair over whole of body, but no pubic or axillary hair. Skin thin. No striæ. Penis and testicles well developed, but not unduly large for his age. Weight 35 lb. 8 oz. Height 32 in.

Cardiovascular system: Pulse-rate 150 per min. Sinus arrhythmia. Soft systolic murmur heard in all areas. Blood pressure 200/140 in arms, 210/150 in legs.

Respiratory system normal.

Abdomen: Grossly obese. Circumference at umbilicus 27½ in. No abdominal organs felt. ? shifting dullness.

Nervous system: Fundi: no vascular changes.

Investigations.—Hb 80%; W.B.C. 13,300 (polys. 57%, lymphos. 33%, monos. 10%). Blood cholesterol 210 mg. per 100 ml. Glucose tolerance test: normal curve, no glycosuria. Urine: less than 0·1 gramme albumin per 100 ml. Plasma sodium 352 mg. per 100 ml. Plasma chloride as NaCl 591 mg. per 100 ml. W.R. negative. Urinary 17-ketosteroids 25.9.52: 1·43 mg. per day. 28.10.52: 2·2 mg. per day. Direct eosinophil counts: several counts below 25 cells per c.mm. Radiographs: Chest, skull, abdomen, and pyelogram normal. ECG. within normal limits.

FIG. 3.—November 26, 1952: Umbilical nodule and striæ.

[Guy's Hospital Photographic Department.]

Subsequent progress.—The child was found to be of normal intelligence for his age. After the first few days he became less sleepy and appeared happy and contented. His blood pressure varied between 200/140 and 145/85, and it was noticed that often when his blood pressure was high he became more sleepy, wet the bed, and refused to talk and play. On November 5, a hard red nodule appeared at the umbilicus (Fig. 3), and on November 12, red striæ appeared on the lower abdomen and upper thighs. His weight gradually increased to 43 lb. 8 oz. On November 22, he was transferred to Guy's Hospital.

Investigations.—24.11.52: Plasma sodium 312 mg. per 100 ml. Serum potassium 13·9 mg. per 100 ml. Serum bicarbonate 67·2 vols.%. Plasma protein 6·73 grammes per 100 ml. Blood urea 40 mg. per 100 ml. 29.11.52: Urine—sugar and albumin present. Urinary 17-ketosteroids 8·4 mg. per day (ketonic) D.H.A. fraction 2·2 mg. per day (normal for an adult).

4.12.52 (post-operative): Plasma sodium 370 mg. per 100 ml. Serum potassium 16·4 mg. per 100 ml. Blood urea 60 mg. per 100 ml.

Operation.—On November 23, his condition began to deteriorate and his blood pressure remained high. For a short while the patient showed an unusual sign, that of flexibilitas cerea—his arm remaining raised when put into that position. He began to develop heart failure, and on November 30 a radiograph of chest showed collapse of the right upper lobe. A biopsy of the umbilical nodule was followed, on December 4, by exploration of the left adrenal gland (Mr. F. N. Glover) as it was thought, on reconsidering the pyelogram, that the left kidney was lower than normal. At operation, the left adrenal gland appeared normal, but a small nodule was found near the gland and a mass was felt within the peritoneum. The gland, nodule, and part of the intraperitoneal mass were excised. Following operation, despite treatment with cortisone and testosterone proprionate, his condition deteriorated and he died on December 9.

Post-mortem examination (Dr. E. A. Wright).—The cheeks, thighs and abdominal walls contained large masses of fat. The omentum contained many pinkish-grey nodules of secondary growth which varied in size from a few mm. to 2 cm. The peritoneum was studded with secondary nodules; no part of the peritoneum was spared, the deposits being especially profuse on the peritoneum lining the anterior abdominal wall and diaphragm. The right adrenal showed extreme autolysis and weighed 8 grammes. The liver was large and very fatty; it weighed 740 grammes and contained secondary deposits. The kidneys appeared normal. The thymus was reduced to only a few nodules of thymic tissue. The heart was enlarged and showed concentric hypertrophy of the left ventricle. The lungs showed bronchopneumonic changes with areas of collapse on both sides. The pituitary appeared normal. There was no evidence of osteoporosis in the clavicles, sternum, and lumbar vertebræ. Histologically the kidneys showed fibrinoid material in only a few of the glomerular tufts; the thymic tissue appeared normal; the pituitary showed no abnormality (Dr. E. A. Wright).

The umbilical nodule and peritoneal secondary deposits were found to be solid alveolar tumours of polygonal cells—probably adrenal cortical carcinomata. The adrenal glands appeared normal (Dr. S. J. De Navasquez).

It is assumed that the adrenal carcinoma arose in aberrant adrenal tissue.

Comment.—The total number of published cases which have come to necropsy is 21, to which the present case is added—making 22. 12 of the patients were girls, and 10 boys. The age of onset of the disease ranged from 11 weeks to 14 years. A basophil adenoma of the pituitary was found in 6 cases, an adrenal carcinoma in 9 cases, an adrenal adenoma in 4 cases, an adrenal tumour of doubtful type in 1 case, carcinoma of the thymus in 1 case, and bilateral hyperplasia of the adrenals in 1 case.

No case of Cushing's syndrome due to a basophil adenoma has been described before the age of 9 years. Only 3 cases, in addition to the present case have been reported in boys below the age of 7 years, and in each instance the cause was a carcinoma of the left adrenal gland.

Epilepsy and Post-gastrectomy Hypoglycæmia.—R. LEWIS, M.B., M.R.C.S.

J. G., aged 52, taxi driver.

He had a partial gastrectomy in January 1951 for dyspepsia of five years' duration. Three months later attacks of palpitations and profuse sweating two to four hours after breakfast commenced

November 1951 admitted to Casualty Department of St. Mary's Hospital having had an attack of major epilepsy. No family history of epilepsy. All investigations, including ventriculography and cerebral angiography were normal. Discharged on phenobarbitone.

Persistent attacks of palpitations and profuse sweating three times a week until November 1952, when he was readmitted to St. Mary's Hospital when he had a second attack of major epilepsy. Insulin sensitivity test (2·9 units soluble insulin I.V.) showed that he was abnormally sensitive to insulin and the conclusion was that he was suffering from post-gastrectomy hypoglycæmia which was precipitating his epileptic attacks.

It is proposed to treat him with a high fat and protein diet with a low carbohydrate content in order to decrease his insulin sensitivity.

Mr. Hermon Taylor said that he had a very similar case to that described. A patient who was known to have a weak personality, and who had had a partial gastrectomy for duodenal ulcer, developed a degree of hypoglycæmia. This had apparently resulted in a marked deterioration of his psychological resistance to the stresses and strains of life. This particular patient had discovered that beer, which is, of course, rich in carbohydrates, was excellent for his hypoglycæmia. He had become almost hopelessly addicted to beer and stronger alcoholics since the operation, with further deterioration of his character.

It seemed that the type of case that had been described added one more risk to the post-operative hazards of partial gastrectomy, namely, the conversion of subclinical psychopathic tendencies into actual disease.

Frozen Popliteal Artery Homograft: A Progress Report (Case previously shown to the Clinical Section on December 13, 1951, and reported in *Proc. R. Soc. Med.*, **45**, 152).—H. H. G. EASTCOTT, M.S., F.R.C.S.

Nine months after his operation this patient suddenly developed pain in his left calf and foot, which became cold. Gangrene developed in the great toe. No pulse could be felt below the groin (Fig. 1). Arteriography showed occlusion of the lower half of the femoral artery.

Left lumbar sympathectomy produced no change.

Operation (1.9.52).—Excision of blocked femoral artery and former graft. The 20 cm. gap was bridged by another frozen arterial homograft, which had been stored for eight months at −79° C.

FIG. 1.—Left foot, following a recurrent thrombosis of the superficial femoral artery above the original graft. Lumbar sympathectomy failed to relieve the pain, coldness and cyanosis in this foot. Gangrene was commencing in the great toe.

FIG. 2.—Left foot, three weeks after operation showing improved nutrition and healing of great toe.

Pulses returned to the foot, which later became hot and throbbed painfully. The gangrenous pieces of skin on the hallux separated.

Arteriography on the tenth day showed the new graft to be functioning well.

Pulses have remained normal since; the patient is fully active (Fig. 2). As an out-patient he is now being maintained on sufficient dosage of dicoumarol to keep the prothrombin activity between 20%–40%.

The histological section of the previous graft showed considerable surviving elastic tissue, and no atheroma or calcification.

I am grateful to Professor C. G. Rob for his help and advice in this patient's management (*see also* 1953, *Proc. R. Soc. Med.*, **46**, 121).

[*January* 9, 1953]

Perniosis, Colitis and Trabeculation of Bladder.—W. A. BOURNE, M.D.

Mrs. E. T., aged 39, developed chilblains when 17 years old.

In December 1950 and February 1951: Bilateral cervical sympathectomy by transthoracic axillary approach (Mr. H. J. McCurrich). Both hands remained warm and dry, but chilblains rapidly recurred.

In April 1951, she became breathless and during the next eighteen months diarrhœa and frequency of micturition developed. She lost 28 lb. in weight. No dysphagia. Amenorrhœa following operation.

She was first referred to a physician in August 1952. Generally pigmented with telangiectases, wasted, with tight lips and small smooth tongue. Atrophic skin over fingers. Afebrile. Sigmoidoscopy: mucosa congested, coppery red to black, appearing almost necrotic. Cystoscopy: bladder capacity 12 pints without discomfort, trabeculation amounting almost to pseudo-diverticula, ureteric orifices and trigone normal, no cause found for trabeculation. Biopsy of quadriceps femoris normal. *X-ray:* Hands: no calcification or bony absorption. Œsophagus and stomach: aerophagy and transient pylorospasm. Small intestines: doubtful deficiency pattern. Lungs normal. ECG. physiological. Renal function: Urea concentration, Specimen 1 : 169 c.c. Urea 0·8 gramme %. Specimen 2 : 61 c.c. 0·9 gramme %. Specimen 3 : 103 c.c. 1·4 grammes %. Specimen 4 : 64 c.c. 1·6 grammes %.

Blood: Hb 88%, R.B.C. 4,590,000. Polys. 36%, lymphos. 61%, monos. 2%, eosinos. 1%. No L.E. cells. E.S.R. and serum proteins normal. Fat absorption and creatinine excretion normal.

Treatment.—Oxamine and mepacrine without benefit. The original suggestion of sclerodermia was not tenable. Much tension became obvious with a history of exaggerated vasomotor response to emotional crises. Colitis occurred when rapid recurrence of chilblains after sympathectomy caused great disappointment. The bladder condition is not understood. Condition of colon and bladder do not correspond with the sclerodermatous lesions described by Cullinan and Kemp-Harper in 1952.

REFERENCE

CULLINAN, E. R., and KEMP-HARPER (1953) In press.

Dr. G. Simon: The demonstration of œsophageal changes by a barium swallow, would place the case in the scleroderma group. These changes may easily be missed if the patient is only examined standing. It is suggested that the œsophagus be re-examined with the patient lying down.

Minor bone changes in the phalanges may also pass undetected, unless each finger is radiographed separately in a true lateral plane.

Traumatic Arteriovenous Fistula.—A. W. NURICK, F.R.C.S., for R. S. HANDLEY, O.B.E., F.R.C.S.

P. G., aged 54.

History.—In 1917, following a gunshot wound of the shoulder, the right axillary artery was tied in its third part. The patient remained well, apart from some limitation of the use of his right hand, until March 1952, when the right arm began to swell and become painful.

On examination.—The right arm was swollen, blue and cold, with pulsation of the superficial veins and a pulsatile swelling in the axilla over which there was a continuous murmur on auscultation.

Investigation.—Using the technique developed for radiological investigation of coarctation of the aorta, a catheter was passed up the opposite (left) radial artery until it lay in the arch of the aorta. 40 c.c. of 70% diodone were injected while pressure was maintained over both carotid arteries. A series of eight X-ray films were exposed during injection.

Early films of the series show the stump of the previously ligated subclavian artery with dilated collateral branches. Later films show an enormously dilated axillary vein and an axillary artery of normal calibre. A tortuous vessel entering the axillary vein proved at operation to be the circumflex scapular artery.

Operation (Mr. R. S. Handley) 14.10.52.—No communication was found between axillary artery and vein, the fistula was between the circumflex scapular artery and the axillary vein via a small aneurysmal sac, and was treated by resection of the dilated segment of axillary vein and ligation of the offending artery.

Progress.—The arm rapidly became pink and warm, the swelling disappeared, and two months after operation the condition was as it had been before the appearance of the arteriovenous fistula, thirty-five years after the original injury.

Spina Bifida with Ulceration of Buttocks.—REX LAWRIE, M.S.

D. H., male, aged 24.

This man was born with spina bifida and was operated on at 3 months for repair of a sacral meningocele. At 7 he began to walk with sticks, but from about 16–20 suffered from ulcers on the buttocks. These had been repeatedly excised and sutured and skin grafted.

In December 1950 he was admitted to Guy's Hospital and the ischial sinuses were again excised and sutured. This time they healed and he was sent to the orthopædic branch, where Mr. F. T. Stamm performed a bilateral triple arthrodesis for talipes calcaneus, which enabled him to walk.

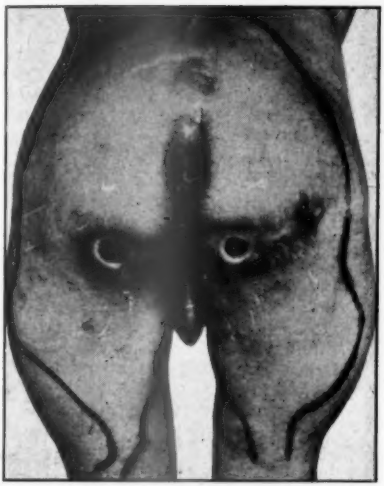

FIG. 1.—Showing the appearance of the chronic ischial ulcers and scars of previous excisions. The scar of the sacral meningocele removed at three months can also be seen. The black lines show the area of anæsthesia.

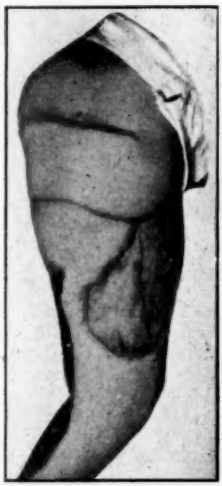

FIG. 2.—Showing the outer side of the right thigh. The flap of skin which has been rotated with the intact lateral femoral cutaneous nerve supply to cover the unsound area of buttock, and the grafted donor site whence it came, can be seen.

After this the right ischial ulcer reappeared and, after three unsuccessful attempts at excision and suture, it was closed by Mr. P. Clarkson who used a rotation flap from the outer side of the thigh, carrying with it the intact lateral femoral cutaneous nerve. The underlying ischial tuberosity was removed.

As a result of this operation he has stable healing of the right buttock with skin which has normal sensation. At the present time he refers the sensation of his right buttock to the outer side of the thigh.

He is now able to walk with two sticks, to hold a full-time job and live an independent existence, which is the goal of every disabled person.

Gastric Hair-ball.—H. H. RENYARD, M.S. (for HAROLD EDWARDS, C.B.E., M.S.).

History.—Miss M. H., aged 17, referred by Dr. Frank Brockington of Camberley. The patient was well until Christmas 1952, when she began to suffer from acute epigastric pain, vomiting and anorexia. She admitted to chewing blankets, sheets and handkerchiefs, and to nail biting as a child. For the past two years she has pulled out hairs and swallowed them. She works as a tracer, and often chews her hair whilst waiting for ink to dry.

On examination.—Well-nourished, healthy-looking girl, who proved very co-operative. A few thin patches on the scalp could be detected. A large abdominal tumour was seen and felt, extending from beneath the left costal margin to the right iliac fossa—a complete cast of stomach (Fig. 1). Hæmoglobin was 74%.

A barium meal and X-ray showed a dilated stomach occupied by a cast of hair thinly coated with barium (Fig. 2).

Discussion.—The word bezoar is derived from the Persian "badzahr" meaning "protection against poison". The Oriental bezoar obtained from the fourth stomach of the bezoar goat of Persia, was greatly prized, and contained resinous and aromatic substances. Bezoars were used as charms and amulets by the Hindus as far back as 1200 B.C., and were often encased in gold and gems, and handed down as heirlooms. A bezoar was included in the inventory of the possessions of Elizabeth I, and it is recorded that another was once exchanged for a Spanish castle. Counterfeits were detected by testing with a red hot needle—the genuine variety did not smoke. Many animals, including the domestic Persian cat and the crocodile, develop bezoars.

In human beings, trichobezoars are found almost exclusively in young females (Morris, 1952), the average age being 15–20 years. Nervous children are common subjects and a high proportion are mental defectives.

Phytobezoars are more common in men and result from ingestion of persimmons, celery, tobacco, coconut and fruit skins. An uncommon variety is that found in French polishers, who might drink their polish for its spirit content and produce a cast of the stomach in shellac. Bezoars are often

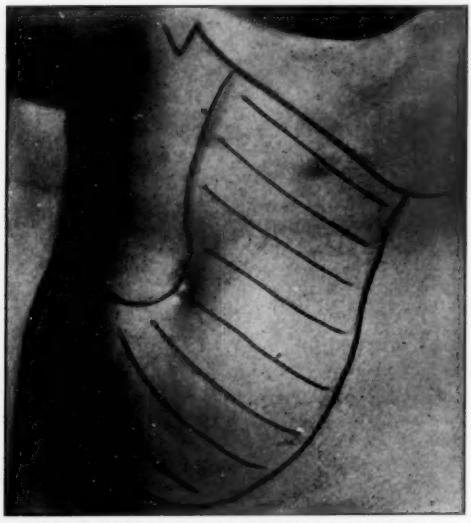

FIG. 1.—The abdomen with the mass outlined.

unattended by symptoms for many years. A degree of gastritis always occurs and ulceration develops in about 10% cases (Aird, 1949). Obstruction, perforation, and hæmorrhage are other complications. The mortality of removal of the foreign body is surprisingly high—nearly 100% if perforation has occurred (Bockus, 1946). The present case is of interest in that despite the enormous size of the bezoar, the patient seems mentally normal and is of good physique and was without symptoms until ten days ago.

Mr. Dickson Wright related the case of a bezoar in a Chinaman who chewed his pigtails since he was forbidden to cut them. Dr. T. Parkinson stated that he had recently examined the crop of a "crop-bound" fowl, and found it full of matted couch grass—a phytobezoar.

ADDENDUM

Operation was performed on 16.1.53.

The stomach was opened along the anterior wall with diathermy, and the bezoar was removed with the aid of midwifery forceps. It showed a clean fracture across its centre. It weighed 1,200 grammes, and was 35 cm.

FIG. 2.—Barium meal showing complete cast of dilated stomach. Note the transverse fracture.

FIG. 3.—The bezoar after removal.

long (Fig. 3). An acute lesser curve gastric ulcer, 2·5 cm. in diameter, was found at the incisura, and this probably explains the recent acute symptoms. Several small sessile overgrowths of the epithelium of the body of the stomach were also found. Section of one of them showed it to have the structure of a simple papilloma. Recovery from operation was uneventful.

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Section of Odontology

President—E. WILFRED FISH, C.B.E., M.D., F.D.S. R.C.S.

[*December* 22, 1952]

The Early Development of Teeth

By C. H. TONGE, M.B., B.S., B.D.S.

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INVESTIGATIONS during the last century have provided considerable information relating to the early development of the teeth.

von Brunn (1887), Röse (1891) and Paul (1896) described the dental lamina, the enamel organ and the differentiation of its cellular elements. More recently Bolk (1921) has studied the enamel organ in a wide range of species with particular emphasis directed to the problems of evolution of tooth form. Wakeford (1926) by means of serial sections of human embryos ranging from 25 mm. to 160 mm. crown rump measurement, has discussed the separation of the lip and the disintegration of the dental lamina, as well as the vascularity and cellular components of the enamel organ. Orban (1928) has made an extensive study of human tooth development and has described the relative growth and movement of tooth germs by measurement and wax reconstructions of embryos of 16 mm. to 217 mm. crown rump measurement. Schour (1929) has discussed the relationship between the dental lamina and the separation of the lip. West (1925) made a comprehensive study of the differentiation of the gum areas in early embryos and traced their growth in relationship to the deciduous dentition.

The object of the present study is to consider the buccal epithelium over the area from which are derived the lips as well as the dental lamina and enamel organ. The differentiation of the mesenchymal tissue, beneath the epithelium of the tooth-bearing area, to which attention has already been directed (Tonge, 1951) is considered.

Material and methods.—The disparity that exists in the literature as to the exact time of initial tooth formation is, in part, due to the difficulty of assessing age in terms of measurement. The problems relating to the estimation of embryonic age have been discussed by many, particularly, Mall (1918) and Streeter (1942–1951).

In embryos between the commencement of the fourth and the end of the fifth weeks counting the somites is a reliable guide to embryonic age. In later stages, in the absence of an exact menstrual history and time of fertilization, estimation by measurement is indicated.

The crown rump measurement, taken from the highest part of the crown to a point mid-way between the projections of the buttock has been used as an index of size of the material examined, which covers an age range of approximately 5½ weeks to 5½ months.

Serial sections of human embryos and fœtuses of the following crown rump measurements have been studied, 7 mm., 11 mm., 12 mm., 15 mm. (3 specimens), 16 mm., 20 mm., 20·5 mm., 24 mm., 25 mm. (2 specimens), 28 mm., 40 mm. (2 specimens), 44 mm., 60 mm. (3 specimens), 71 mm., 90 mm., 100 mm. (3 specimens), 110 mm., and 190 mm. Since the range is made up of specimens cut sagitally, coronally and transversely a composite picture of the developing buccal epithelium and mesenchymal tissues was obtained.

Many staining techniques in common use have been employed (*see* Cowdry, 1948). Mallory's connective tissue stain contrasts the epithelial tissues, developing bone, cartilage and fibrous tissue suitably for microscopic examination. Methylene-blue and some silver stains, however, are preferable if black and white photographic reproduction is desired. Foot's reticulum stain and Van Gieson's connective tissue stain have also been employed.

Observations

The buccal epithelium.—The 7 mm. embryo shows flat nasal placodes without the formation of nasal pits, the otic vesicle has lost its connexion with the surface and the cervical sinus is in the process of formation. The lingual swellings and tuberculum impar are still separated, the lung bud has formed two short bud-like projections without any lobulation. Rathke's pouch is shallow as it projects from the primitive buccal cavity to the region of the developing fore-brain.

In attempting to demonstrate the position of the future tooth-bearing area of the buccal epithelium, each jaw has to be considered separately. In the lower jaw the lingual swellings are flat elevations separated by a furrow, so that, as the tongue area is not yet defined, it is impossible in the lower jaw to localize a tooth-bearing region with any degree of accuracy. The general zone of buccal epithelium can be isolated. In the region corresponding to the future upper jaw the nasal placodes are present with the area representing the future median nasal process between them. This area of the median nasal process is extending in depth into the primitive buccal cavity and is forming its roof. The buccal epithelium covering the median nasal process can be traced as a continuous layer into the developing buccal cavity and the tooth-bearing area of the future premaxillary region defined with accuracy, since the median nasal process contributes to the development of the premaxillary area.

The buccal epithelium of the 7 mm. embryo is of the low columnar type with chromatin-rich nuclei and cellular boundaries between the adjacent cells (Fig. 1). The surface epithelium from the region of the scalp shows some specialization and is composed of a single layer of flat cells with chromatin-poor nuclei, having no cellular boundaries and forming a surface syncytium (Fig. 2).

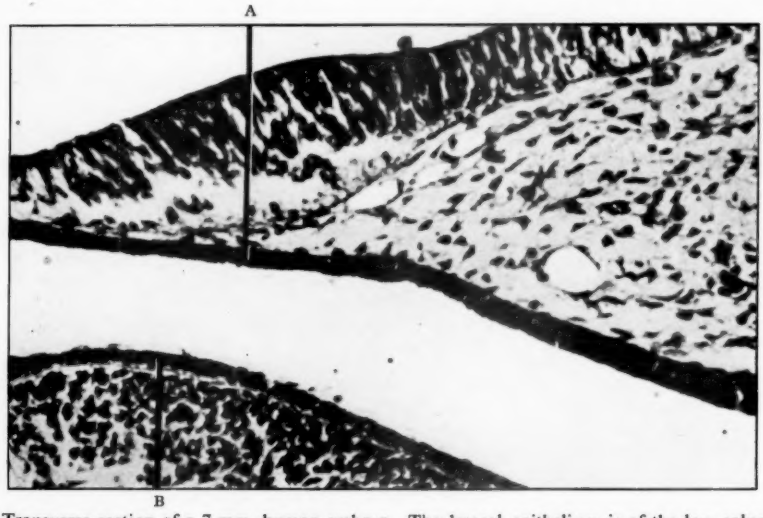

FIG. 1.—Transverse section of a 7 mm. human embryo. The buccal epithelium is of the low columnar type (A) Epithelium of fronto-nasal process. (B) Epithelium of the mandibular process. × 146.

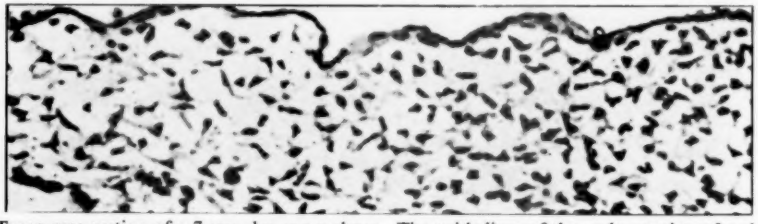

FIG. 2.—Transverse section of a 7 mm. human embryo. The epithelium of the scalp consists of a single layer of flat cells with no definite cellular boundaries. × 153.

The presence of a few cells lying on the surface of the basal low columnar cell layer of the buccal epithelium was first observed in the 12 mm. embryo. In comparison the surface of the scalp and future chest wall consists of flattened cells with cellular boundaries that are now becoming distinctive; whilst, beneath the surface there is a vascular mesenchyme containing a loose cellular reticulum.

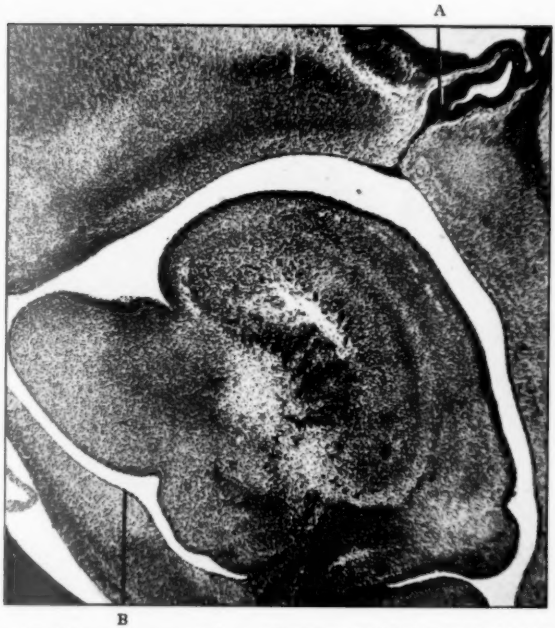

FIG. 3.—Sagittal section of a 16 mm. human embryo. The buccal epithelium and (A) the outgrowth forming the anterior lobe of the pituitary gland can be seen. The early chest wall (B) is also seen. × 9.

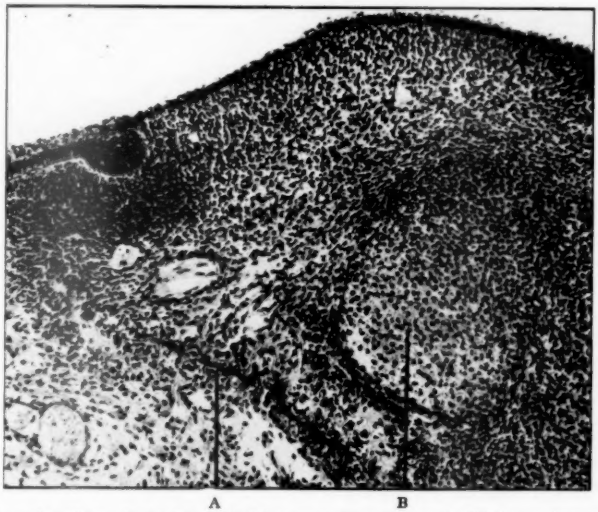

FIG. 4.—Coronal section through the lower deciduous canine region of a 20·5 mm. human embryo. Several layers of flattened cells can be seen forming on the surface of the columnar buccal epithelium. A well-marked diffuse area of mesenchymal condensation is seen beneath the epithelium of the tooth-bearing area. (A) Developing mandible. (B) Meckel's cartilage. × 103.

In the 15 mm. and 16 mm. embryos a low columnar epithelium is seen lining the area in both jaws which later differentiates to form the lips, teeth and gums. A zone of more rapid proliferation is found forming the epithelial or dental band from which are derived the tooth buds. The epithelium

is arranged in some 5–8 layers in depth in the incisor region and 3–5 layers in the molar region. The thickness of the epithelium and the heaping up of flattened cells on the surface in the region of the dental band can be seen in Fig. 3 and compared with the thin surface layer of the future chest

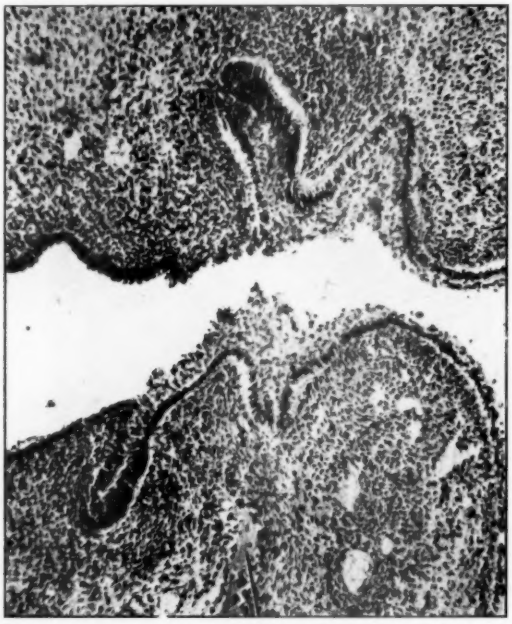

FIG. 5.—Oblique coronal section through the incisor region of a 24 mm. human embryo. (A) Developing mandible. × 117.

FIG. 6.—Sagittal section to the right of the mid-line through the lower central incisor tooth germ of a 60 mm. human fœtus. (A) Meckel's cartilage. × 12.

wall to the left of the field. The buccal epithelium lines the roof of the primitive oral cavity and can be traced into Rathke's pouch from which is derived the anterior lobe of the pituitary gland. A common epithelium is seen, therefore, developmentally in regions where adamantinomata are found (Fig. 3).

The gradual increase in the surface layers of flattened cells upon the proliferating columnar epithelium occurs progressively and can be observed in the 20·5 mm. stage (Fig. 4), the 24 mm. stage (Fig. 5), and the 60 mm. stage (Fig. 6).

The heaping up of the cellular elements superficial to the basal columnar epithelium as a prelude to keratinization is restricted to the lips, cheeks, vestibule of mouth, labio-buccal gingival area and site of origin of the dental band from the surface. The lingual and palatal portions of the developing gingivæ do not show this accumulation of flattened cells upon the surface of the columnar epithelium.

In Fig. 6 the extent of the buccal epithelium with its 10–30 layers of prickle cells with nuclei present in most of them can be observed. Progressive flattening and loss of cellular detail is apparent as the surface is reached.

In the 90 mm. and 100 mm. specimens keratinization could be observed in the cutaneous part of the lip, the labial mucosa and the labio-buccal part of the gingival mucosa. Evidence of desquamation of the surface elements of the keratinized area was seen in the 100 mm. stage and the 190 mm. stage (Fig. 7).

The irregularity of the labio-buccal part of the gingivæ as compared with the lingual part and its division into segments corresponding to each of the deciduous teeth first, observed by West (1925), is confirmed and the villous appearance of the labio-buccal gum area can be seen in Fig. 7. The lingual area of the gum shows no evidence of accumulation of flattening layers of cells upon its surface, no keratinization. It is similar to the epithelium found on the undersurface of the tongue (Fig. 7). The transition between the labial mucosa, the cutaneous part of the lip and the skin proper with its developing hair follicles is also seen in Fig. 7.

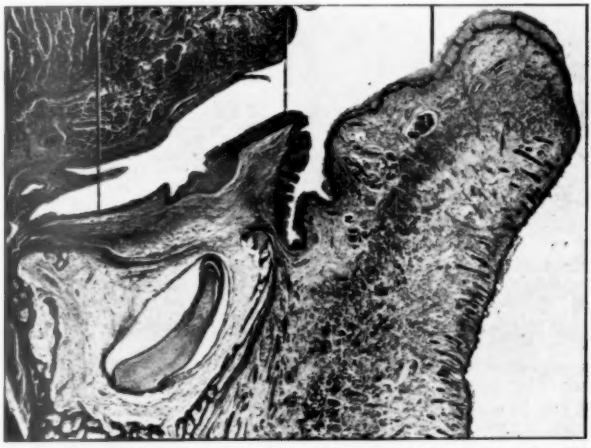

FIG. 7.—Sagittal section through the lower jaw, floor of mouth and lip region of a 190 mm. human fœtus. Keratinization can be observed over the whole of the potential tooth-bearing area of the gingival region and the labial mucosa contrasting with the cutaneous area of the lip and the skin with its developing hair follicles. The villous arrangement of the labial gingiva contrasts with the flattened lingual gingiva. (A) Lingual gingiva; (B) Labial gingiva; (C) Labial epithelium. × 16.

THE MESENCHYMAL TISSUES

A reaction on the part of the mesenchymal tissues to the activity of the buccal epithelium was not observed earlier than the 12 mm. specimen. At this stage there is an ill-defined and diffuse condensing of the cells beneath the columnar epithelium of the tooth-bearing area, although there is no evidence of histo-differentiation of the mesenchymal cells.

A diffuse condensation of the mesenchymal cells extending beyond the limits of the epithelial invagination can be seen in the 15 mm., 16 mm., 20 mm., and 20·5 mm. embryos and is illustrated in Figs. 3 and 4.

A gradual alteration in the relative extent of the mesenchymal condensation can be observed in association with the progressive invagination of the surface epithelium and the separation of the lip. In Fig. 4 the condensed area extends labially as far as the plane of the developing mandible projected

to the surface, which corresponds to the limit of the labial gingivæ. It is continued, in addition, into the lingual part of the gingiva.

The progressive differentiation of this mesenchymal condensation to form the dental papilla, the dental follicle and the supporting connective tissue of the gingivæ can be seen in the later stages (Figs. 5, 6 and 7).

In the earlier stages the mesenchymal tissue of the dental papilla, dental follicle and gingival area blends with the periosteal layer covering the developing alveolar bone (Figs. 4 and 5). The separation and isolation of the dental papilla and dental follicle is seen to be associated with the growth of the tooth germ and the bony socket in which it is contained (Figs. 6 and 7).

Conclusions

The epithelium of the buccal cavity has at a very early stage, 7 mm., an appearance different from that of the future skin of the chest wall and the scalp. The buccal epithelium is of a low columnar type with distinct cellular boundaries; whereas, the surface of the scalp or of the chest wall shows some specialization and is lined by a single flattened layer with no cellular boundaries until the 12 mm. stage is reached.

The buccal epithelial lining is contributing to the anterior part of the pituitary gland and the salivary glands, as well as the epithelial component of the dental tissues; a connexion, in early development, between adamantinomata of the pituitary and the jaws is thus established.

The buccal epithelium progressively shows the presence of a surface accumulation of flattened cells upon its basal columnar layer. Keratinization was observed in the later stages over the whole of the potential tooth-bearing area of the lips, cheek, vestibule of the mouth and extending as far as the area separating the labial from the lingual or palatal portions of the gingivæ.

The mesenchyme in the early stages of development forms a condensed mass beneath the epithelial part of the tooth germ. This mesenchyme gradually differentiates into the dental papilla and dental follicle and forms the supporting connective tissue of the alveolar socket and gingivæ.

When viewed from a comparative study of vertebrates the mouth is essentially an invagination from the exterior to the pharynx. It has a surface epithelial lining and mesenchymal supporting tissue. The general evolution of teeth has been from a loosely attached larger number of conical teeth, associated with any region of the mouth, to a reduced dentition firmly fixed within alveolar bone in a specific part of the mouth. This reduction in the dentition and alteration in its attachment is associated with a progressive evolution of the tongue, the palate and the separation of the lips. The area between the junction of the labio-buccal and lingual parts of the gums and the buccal epithelium of the cheeks and lips is, therefore, to be regarded as potentially tooth-bearing. It is not surprising, therefore, to find the buccal epithelium behaving in a similar manner over this potential tooth-bearing area in the phases associated with early tooth development in the human.

Summary

The majority of the work published on the early development of the human teeth is concerned with the formation of the dental lamina, tooth germs and the separation of the lip. The present study lays emphasis on a consideration of the buccal epithelium as a whole, which from an evolutionary viewpoint can be regarded as potentially a tooth-bearing area. The arrangement of the mesenchyme beneath the buccal epithelium is described in relationship to its later differentiation.

Material and methods.—Serial sections of 26 human embryos and fœtuses, ranging from approximately 5½ weeks to 5½ months with crown rump measurements from 7 mm. to 190 mm. have been examined.

Observations.—(1) The area of the primitive buccal cavity can be localized in the 7 mm. human embryo. The buccal epithelium is of a low columnar type and differs from that of the scalp or chest wall which is formed by a single flattened syncytium.

(2) The buccal epithelium of the potential tooth-bearing area shows surface proliferation in the earlier stages as a prelude to keratinization and desquamation by the 100 mm. stage.

(3) The mesenchymal condensation observed beneath the epithelial invagination of the early embryos differentiates into the dental papilla, dental follicle and supporting gingival connective tissue of the later fœtuses.

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Section of Pathology

President—Professor G. PAYLING WRIGHT, D.M., F.R.C.P.

[*January* 20, 1953]

Nerve Trunks as Pathways in Infection

PRESIDENT'S ADDRESS

By Professor G. PAYLING WRIGHT, D.M., F.R.C.P.

THE routes and mechanisms by which micro-organisms and their toxic products may be disseminated in the body have presented many problems of great interest to pathologists. For manifest reasons, such studies have centred mainly on the circulating fluids in blood and lymph vessels, but evidence has gradually strengthened that in some infectious diseases other pathways may assume a more dominant role. The great nerve trunks of the body provide far-reaching connexions between vulnerable peripheral structures and the central nervous system, and it is hardly surprising that early in the study of the pathogenesis of infections of the brain and spinal cord, suggestions should have been made that noxious agents could pass centripetally by these routes. As with many subsequently fruitful concepts, early expressions of the belief that nerves might serve for the conveyance of such material agents as well as of nervous impulses, took the form of nebulous suggestions. In his historical account of the growth of ideas on the movements of viruses and toxins in peripheral nerves, Doerr (1936) attributes to Krügelstein, whose monograph on rabies appeared in 1826, the first mention of a possible ascent of the noxious agent along a nerve trunk. With diseases that bear such obvious resemblances as rabies and tetanus—their typical appearance after bites and wounds and their main signs dramatically focused on the nervous system—it is hardly surprising that parallels were drawn as to their pathogenesis. Thus in 1836, in his well-known "Treatise on Tetanus", Curling discusses rabies and tetanus and remarks that the noxious agent "is confined for an indefinite time to the nerves of the part injured, being transmitted at some subsequent period to the medulla (spinalis), and thus exciting the disease". It is clear that the idea that nerve trunks form potential conductors of pathogenic agents to the brain and spinal cord had already found a place in Pathology more than a century ago.

The Structural Components of Nerve Trunks which might serve as Conduits

Histological examination of any large nerve trunk shows that within its outer tunic—the epineurium—are several discrete nerve bundles, each of which in turn is surrounded by a layer of connective tissue termed the perineurium. These successive fibrous sheaths thicken as the spinal cord is approached, but their existence can still be made out in the distal ramifications of the trunk. Inside the perineurium, and supported by the delicate connective tissue of the endoneurium, lie the nerve fibres themselves, each enclosed in its myelin sheath, Schwann cell envelope and fibrillary neurilemma.

Lymphatics as potential conduits.—There are few accounts of the occurrence of lymphatics in the larger nerve trunks. Defrise (1930) failed to find endothelial cell-lined channels inside the perineurium—all such vessels were contained within the substance of the epineurium. Stöhr (1928) bluntly stated that nerve trunks contain no lymphatics internal to their perineurium, but gave no supporting references. The clarification of this morphological point is important for the present problem, because the assumption has sometimes been unjustifiably made that substances carried along neural lymphatics eventually reach the subarachnoid space of the spinal cord. Abel and his colleagues have been at pains to dispel this error (Abel, Evans, Hampil and Lee, 1935; Abel, Hampil and Jonas, 1935). They emphasized that the only true lymphatics of nerve trunks lie outside the perineurium, and that these are no exception to the general rule for such vessels in that, as they approach the vertebral column they unite to form collecting channels which converge on the regional lymph nodes.

While it now seems that no direct pathways link the epineural lymphatics with the subarachnoid space, injection studies made recently by Brierley and Field (1948; Field and Brierley, 1948*a*, *b*) have disclosed the possibility of connexions of a more devious kind. They found that when finely divided indian ink particles are injected into the subarachnoid space, they collect in black aggregates in the arachnoid culs-de-sac round the emergent nerve roots, and may be traced thence to the prevertebral lymphatics. Since the direction of flow of fluid in these minute channels is determined by pressure differences between the subarachnoid space and the abdominal lymphatics, it may be assumed that any flow ordinarily takes place from the former to the latter. The assumption that noxious or

other material can be conveyed from the periphery to the spinal theca by lymphatics thus implies that at times a retrograde flow can develop along these small, newly observed, connecting channels. Brierley and Field have been able to induce such a reversal of flow by raising the pressure in the abdominal lymphatics to about 15 mm.Hg, a value which is unphysiological but by no means inconceivable in pathological states. Under these abnormal conditions, ink particles can pass from the pre-vertebral lymphatics to the dorsal root ganglia and near-by theca. From anatomical studies, therefore, it seems that while the neural lymphatics provide no direct pathway to the spinal theca, circuitous routes may be opened should the usual pressure gradient between the subarachnoid space and the abdominal lymph trunks become reversed.

Tissue spaces between individual nerve fibres.—Carefully to be distinguished from the lymphatics proper are the tissue spaces that lie between the separate nerve fibres. These are the homologues of the tissue spaces found elsewhere in the body, though in their great uninterrupted length and almost unvarying calibre they possess two features that render them unique. It is difficult to determine by direct measurements on histological material what proportions of the cross-sectional area of a nerve trunk are occupied by fibres and by tissue spaces respectively, because of the shrinkage errors associated with the technical treatment of the tissue. Recent observations by Causey (1948), however, provide data from which an estimate is possible. His experiments were designed to examine the effect of pressure, applied externally by a mercury sleeve to a nerve trunk, upon the size of the individual fibres. Since the compressed length of nerve and the uncompressed parts above and below were all later prepared for histological examination by the same method, it is reasonable to assume that shrinkage errors did not invalidate their subsequent comparison. The effect of the pressure on the over-all size of the trunk can be well seen in the photomicrographs that Causey has published (*see* Fig. 1). It is possible,

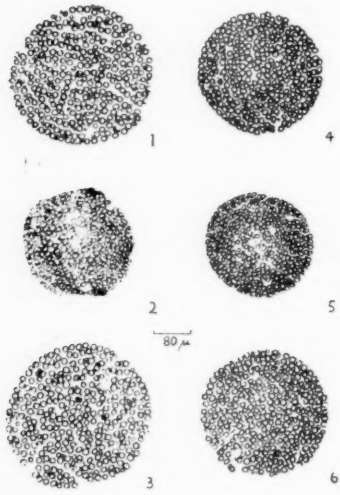


FIG. 1.—The effects of pressure applied externally upon the size of nerve trunks and their constituent fibres. Nos. 1, 2, 3 and 4, 5, 6 are photomicrographs of transverse sections (stained with Weigert-Pal's method) of the nerve to the medial head of the gastrocnemius muscle of two rabbits; in the former a pressure of 560 mm.Hg and in the latter one of 150 mm.Hg was applied for ten minutes at sites 2 and 5 respectively. (*From* Causey, 1948, with permission.)

however, to proceed further with this data and extract from it the different proportions to which this compression is borne by the fibres and the other parts of the trunk respectively. In Table I, I have set out in summary form the varying degrees to which the whole trunk and its constituent fibres shrink under external pressure.

TABLE I.—SHRINKAGE OF RABBIT'S NERVE TRUNK AND NERVE FIBRES UNDER COMPRESSION (*From* Causey, 1948)

Pressure (mm.Hg)	Time (min.)	Percentage of original size	
		Nerve trunk	Nerve fibres
150	10	71	82
560	15	63	77

Causey's observations show that both the trunk as a whole and its individual fibres shrink with compression, but the former more so than the latter. Such a proportionate difference can happen only if a large fraction of the interior of a normal trunk is occupied by some expressible tissue fluid lying in its interstices; the clefts between the fibres must therefore be accepted as *real* and not as merely *potential* spaces. How slight is the mutual adhesion between the fibres can also be appreciated from the readiness with which these orientated channels open up to provide a passage for fluids injected directly into the interior of the trunk (Fig. 2). The same ease of separation can also be seen

in sections of œdematous nerves or trunks undergoing infiltration with neoplastic cells. Later on, I shall discuss evidence that under natural conditions these spaces can serve as conduits for centripetally moving fluid.

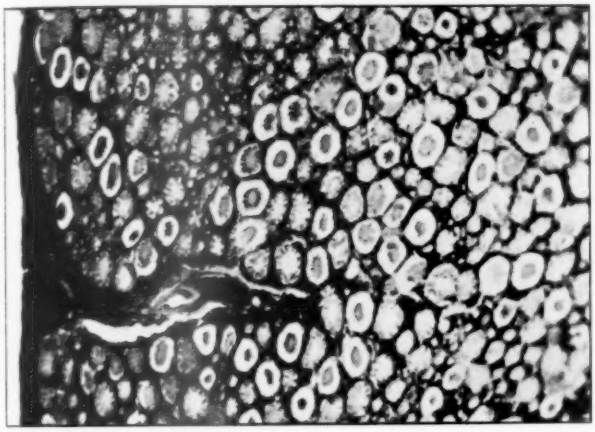


FIG. 2.—Transverse section of the sciatic nerve of a rabbit above the site of an intraneural injection of indian ink, showing the carbon particles in the spaces between the individual nerve fibres.

The axons.—Last amongst potential conducting pathways in the trunk are the axons themselves. These cytoplasmic filaments vary in diameter from one to twenty microns, and form strands of protoplasm which run without interruption from the brain or spinal cord to distal terminations in sensory and effector organs. It is unquestionably this element of continuity that has inclined so many investigators to regard them as the most likely conduit for conveying neurotropic viruses and toxins over long distances. Two aspects of the intimate structure of the axon at present concern us: firstly, the physical consistence of its contents, and secondly, the possibility that it may contain formed elements that might promote or retard the passage of material along its interior.

De Rényi (1929) examined the consistence of axoplasm in both the relatively small nerve fibres of vertebrates and the larger ones of some invertebrates. With the former, he was able to strip its sheath from the axon with microdissection needles—a procedure which revealed the latter as a gelatinous strand which, even after being torn into lengths, still retained a rod-like shape. If a rent were made in such an axon, no fluid was seen to escape from the site of rupture. De Rényi reached the conclusion that vertebrate axons have a semi-solid consistence such as would preclude the likelihood that any of its protoplasm could stream along the fibre. On the other hand, he found that the axons of the larger invertebrate nerves contained a viscous fluid resembling egg albumen in consistence. When he punctured its membrane, the axoplasm flowed slowly out into the surrounding fluid. This escape of axoplasm could be detected because it contained fine refractile granules, which could be seen to approach from near-by reaches of the fibre and to emerge at the hole made in its membrane; this observation strengthened his belief in the fluid nature of invertebrate axoplasm. It is needful to point out these differences in the consistence of the axoplasm in the nerves of different species because, largely by reason of experimental advantages attaching to their relatively enormous diameters, neurophysiologists have recently given much attention to the giant fibres of some invertebrates. De Rényi's observations have shown that caution must be exercised before these latter findings are applied without reservation to the structure of the vertebrate neuron.

The possibility that axons possess some internal fibrillary structure was advanced more than a century ago, and has ever since provided a notable field for controversy in neurohistology (*see* reviews by Parker, 1929, and by De Rényi, 1932). Recently, mainly by the aid of electron-microscopy, further attempts have been made to clarify a problem in morphology that has long defied ordinary visual methods. Unfortunately, an approach which at first seemed promising has yielded little result. The necessary techniques still require both fixation and desiccation of tissues preparatory to observation—procedures which are naturally suspect in any search for the ultramicroscopic structure of living cells. Moreover, the recent recognition by Schmitt and Geren (1950) that the structures they had regarded and described as "neural tubules" were artefacts which had arisen from contamination with connective tissue fibrils from the sheath has cast a shadow over most of the earlier studies.

To summarize, all that can at present be inferred about the possibility that vertebrate axons may serve as conduits for the ascent of toxins and viruses, is that while no internal structures have yet been found that might prove insuperable obstacles to such movements, the semi-solid, or at least highly viscous, consistence of their protoplasm discourages any belief that foreign material can be carried for long distances in relatively short times by streaming or circulation of the axoplasm.

Nerve Trunks as Pathways for the Centripetal Movement of Fluid

From this brief summary of the structural elements of nerve trunks, I shall now turn to review from a more dynamic standpoint the evidence that they provide a pathway for the centripetal movement of tissue fluid and of any foreign material dissolved or suspended in it. This problem has been attacked by many investigators, and it is natural that most of them should have adopted the apparently simple approach of observing directly any displacement of some coloured or radio-opaque material injected beneath the perineurium of some major trunk such as the sciatic nerve of the rabbit. Such experiments have been justly criticized on several grounds. It has often been pointed out that much of any shift might well have resulted from the act of injection itself. In such studies, it is sometimes forgotten that the application of a subjectively small force to the plunger of a tuberculin syringe generates pressures, even at the orifice of the needle, that are far in excess of any ever present physiologically in the tissues. The ease with which indian ink can be propelled along a large nerve trunk shows how easily it can be made to serve as an artificial conduit, but it provides no demonstration that under physiological conditions its tissue clefts contain a current of fluid. Moreover, some of these studies are vitiated from the start by the relatively enormous volumes of fluid injected. To force 200 c.mm—sometimes even 500 c.mm.—of fluid into a rabbit's nerve trunk about 1 mm. in diameter, and already largely occupied by its own nerve fibres, is a travesty of experimentation. Further, the choice of injection fluid has not always been happy. Dyes readily become attached to tissue components and immobilized accordingly, suspensions tend to conglutinate and form obstructive masses, while radio-opaque oils have much higher viscosities than the natural tissue fluids. Attractive though the use of intraneurally injected coloured materials may seem, the method is too crude in design to contribute effectively to answer the prime question: How can foreign material be carried in nerve trunks for long distances from some distant site in the tissues to the central nervous system?

To gain an insight into this problem, it is essential, I believe, to introduce the foreign material into the tissues innervated and not into the interior of the regional nerve trunk itself. The operative procedures entailed by intraneural injections into such trunks as sciatic nerves in rabbits inevitably cause serious disturbances in these small delicate structures at the very time when they should be maintained under conditions as nearly physiological as possible. It is important also to use some indicator material whose presence can still be detected even though, through admixture with tissue fluid, it may only be present in the tissues at a high dilution. Such stipulations severely reduce the number of acceptable agents. I shall discuss two: (1) radio-tracer marked homologous proteins, and (2) the exotoxin of tetanus.

(1) The use of radio-isotopes for marking purposes makes it possible to carry out experiments such as the following in which both small volumes of inocula are needed and minimal trauma inflicted. Wright, Morgan and I have found that if a small volume of a solution of lightly radio-iodinated rabbit's serum proteins is injected into the calf muscles, it is possible to trace the subsequent ascent of the radioactive material along the sciatic nerve trunk. In Table II are shown results from rabbits

TABLE II.—RADIOACTIVITY OF GASTROCNEMIUS MUSCLES AND SCIATIC NERVES OF RABBITS AFTER INJECTION OF ^{131}I-RABBIT SERUM PROTEIN INTO LEFT GASTROCNEMIUS

Hours after injection	Gamma counts per min. per gramme tissue			
	Gastrocnemius muscles		Sciatic nerves	
	Left	Right	Left	Right
3	205	1	232	18
6	105	1	1140	30
12	145	1	130	0
24	69	1	256	0

(Wright, E. A., Morgan, R. S., and Wright, G. Payling, unpublished observations.)

killed at various intervals after inoculation, the radioactivities of whose excised regional muscles and nerves were separately determined. To exclude the possibility that the radioactive material might have been widely distributed to other parts of the body by the circulation, control determinations were made on the corresponding muscles and nerves of the opposite hind-leg. It can be seen from this table that the radioactivity of the muscle at the inoculated site tends to fall progressively during the ensuing twenty-four hours. Meanwhile, that of the sciatic nerve, taken as a single undivided trunk, rises at about six hours to a maximum which was materially higher than the value found at this time for the inoculated muscle. The simplest explanation for this finding seems to be that the sciatic nerve trunk is acting as a conduit for the escape of the marked material.

While these results support the belief that soluble material inoculated into a relatively large and active muscle ascends its motor nerve trunk, they admittedly provide no proof that this transference takes place along the tissue spaces inside the perineurium rather than through the true lymphatics in the epineurium, which, during dissection, are necessarily removed together with the nerve trunk itself. However, it may reasonably be advanced against this latter possibility that pieces of muscle

removed from the thigh on the same side, which presumably also contained lymphatic vessels running centrally from the inoculated site, displayed comparatively little radioactivity.

(2) I shall consider the evidence for centripetal neural transmission of tetanus toxin in greater detail for two reasons: firstly, because many of our ideas about this mode of dissemination of pathogenic agents in the body developed originally from attempts to explain the remarkable regional limitations of the characteristic spasticity of local tetanus in man and animals, and secondly, because the interpretation of the innumerable experiments carried out with this fascinating toxin has provided some of the most controversial literature in bacterial toxicology.

I shall begin with a quantitative consideration which seems to me to be of paramount importance for understanding the pathogenesis of local tetanus in a susceptible animal such as the rabbit—the almost homœopathic dose of the toxin needed to evoke striking spasticity in an affected limb. In some experiments, we could produce hind-limb tetanus consistently by inoculating a solution which contained 100 µg. of our dried toxin into the calf muscles. From the comparative lethalities of this preparation and of the highly refined one made by Pillemer and his colleagues (1948), it seems probable that one-five-hundredth of our fairly active dried material is actually toxin. Even though this fraction is only roughly evaluated, it gives an indication of the order of difference in potency between the two toxin preparations. It thus transpires that the full syndrome of local hind-limb tetanus in rabbits can develop forty-eight to seventy-two hours after the injection into the calf of less than 1 µg. of active toxin—perhaps much less, for Pillemer's preparation may still contain inactive ingredients. No other material has yet been used to study fluid movements in nerve trunks that is able to register effects in such minute amounts. Mulder (1938), who criticized trenchantly the tendency of former investigators to use excessive quantities of dyes and other materials in intraneural injections, himself never used less than 250 µg. of potassium ferrocyanide, and more often he used 10,000 µg. in his inocula. It is this exceptional ability of tetanus toxin to register effects that places it in a widely different category from any other soluble material hitherto used in the study of this problem.

Evidence for the centripetal movement of tetanus toxin in regional nerve trunks has been collected over more than half a century by many investigators. It would take too long now to review the many contributions of those authors who have felt satisfied that their experimental findings could best be accounted for on this hypothesis. It would seem better to examine and test the strength of some of the objections that have been raised against it.

In recent years, the strongest criticisms of the nerve-carriage theory for this toxin have come from Abel and his colleagues at Baltimore, who have turned back to the old idea of Vaillard and Vincent (1891) that local tetanus is essentially an intoxication at the regional myoneural structures. To guard myself from any charge of lack of objectivity in summarizing their views on this controversial matter, I will quote the relevant extract from Topley and Wilson (1946, p. 1753). "Briefly, these workers object to the hypothesis of axis cylinder carriage on the ground that (1) there is no evidence to show that the axis cylinders ever contain tetanus toxin; (2) there is no known mechanism that will explain how the toxin is transported in the axis cylinders, often for long distances, to the central nervous system; (3) the injection of a sub-lethal dose of toxin directly into the sciatic nerve of the dog does not give rise to tetanus, provided measures are taken to prevent the escape of the toxin into the surrounding tissues; and (4) the injection of antitoxin into the sciatic nerve, provided none leaks into the surrounding tissues, does not prevent the development of local tetanus after injection of toxin into the muscles of the leg. A second hypothesis, which has been held by some workers, that the toxin is carried to the central nervous system by the endoneural and perineural lymphatic vessels, seems to be ruled out on anatomical grounds." I shall consider these objections, which Abel applied equally to all theories of nerve trunk carriage, in the reverse order from that given in this quotation.

I have searched the Baltimore publications carefully for experimental evidence that the proximal intraneural injection of antitoxin fails to prevent the onset of local tetanus after a distal intramuscular inoculation of the toxin. This failure in prophylaxis runs directly contrary to the success of Meyer and Ransom (1903), Sawamura (1909), Permin (1914), Teale and Embleton (1920) and others in experiments of this design. Abel's evidence (*see* Abel, Firor and Chalian, 1938, p. 383) appears to be condensed into a single representative protocol in which it is stated that 6 c.mm. of a diluted antitoxin solution were injected high into the sciatic nerve trunk of a dog, and that toxin, in doses one-sixth the immunological equivalent, was injected simultaneously into the muscles of each lower leg. Four days later, local tetanus appeared in both hind-limbs. In this experiment, Abel seems tacitly to have assumed that whatever happened to the toxin, the antitoxin would be retained at the site of its inoculation, and to have drawn the inference that the toxin could not have ascended to the lumbar cord along the sciatic nerve trunk because his small inoculum of antitoxin barred this pathway. But if the toxin moves in this direction, so does the antitoxin, as we have shown in experiments in which the lumbar cord was protected against intoxication even though the antitoxin was injected into the sciatic nerve on the opposite side. The most reasonable explanation for this finding of Abel and his colleagues would seem to be that both the antitoxin and the toxin had moved centripetally—the former well in front of the latter—and that by the time that the toxin had reached the lumbar cord in his dogs several days after its inoculation, the antitoxin, initially in slight excess but with no

comparable affinity for nerve cells, had become so diluted and dispersed elsewhere in the body that it no longer sufficed to prevent the regional intoxication of the cord.

The assertion by Abel and his associates (Abel, Hampil and Jonas, 1935) that an injection of a sub-lethal dose of tetanus toxin into the sciatic nerve is not followed by local tetanus is opposed to the observations of many previous investigators and is difficult to reconcile with their own protocols. In Table III, I have summarized their relevant data, arranging the dogs in order of decreasing dosage

TABLE III.—ABEL'S EXPERIMENTS ON INJECTION OF TETANUS TOXIN INTO SCIATIC NERVES (*From* Abel, Hampil and Jonas, 1935)

Dog number	Toxin (m.l.d.)	Result on leg	Post-operative treatment (where recorded)
S 3	1/2	"stiffness"	
S 4	1/4	,,	Movement restricted by cage
S 5	1/8	,,	
S 6	1/8	,,	
S 8	1/9	,,	
S 7	1/17	none	Movement restricted by cage
S 1	1/48	,,	
S 9	1/50	"stiffness"	
S 10	1/50	,,	Ran freely in paddock
S 11	1/50	none	
S 12	1/50	,,	
S 13	1/50	,,	
S 14	1/50	,,	

of toxin used. It can be seen here that more than half of these 13 dogs whose sciatic nerves had been injected with toxin developed stiffness of their limb, and that there is a good correlation between the appearance of this sign of tetanus and the size of the inoculum. Furthermore, the immediate post-operative treatment of the dogs appeared to influence the course of the intoxication: those animals that were, to use their words, "placed in a cage in order to restrict activity" seemed less likely to develop stiffness than those which were "allowed to run free in the paddock". The significance of such differences in the freedom of exercise permitted after inoculation will be more apparent later when the effect of contraction of a muscle on the pressure of its tissue fluids is considered. From an examination of these detailed protocols, I am unable to accept Abel's contention that the injection of toxin into the sciatic nerve is not followed by local tetanus.

Conspicuous amongst the arguments levelled by Abel and his colleagues against the view that tetanus toxin is carried centripetally through the tissue spaces of motor nerve trunks has been his contention that "the tissue pressure at peripheral points is not of sufficient magnitude to move solutions through such narrow spaces" (Abel, Evans, Hampil and Lee, 1935, p. 107). He emphasized this when he stated (Abel, 1934, p. 123): "We should have to take into consideration known facts in respect to the pressure of the cerebrospinal fluid which in the lumbar theca of a man in the recumbent position varies from 80 to 120 cm. (this is presumably an error—it should be mm.), in terms of Locke's solution, and then enquire whether an individual with the natural disease, say of the foot, would ever develop such an enormous increase of the normal tissue pressure of his foot (2 to 6 cm.) as would be necessary to propel the toxin from the foot to the subarachnoid spaces of the cord—even if there were a direct and open pathway or channel to the cord." It is clear from this extract from one of his papers, that Abel was unaware of the heights to which tissue fluid pressures can rise even under quite ordinary circumstances. Drinker and Field (1933) recorded the pressure in an unobstructed lymph trunk in a dog's hind-leg, and found that when the limb was passively flexed and extended, it rose to over 600 mm. of Locke's solution—that is some five to seven times Abel's estimate for that of the cerebrospinal fluid. With active exertion, the tissue pressures in the belly of a muscle may rise much higher. Barcroft and Dornhorst (1949) found that in voluntary contractions, the calf muscles in man are able to expel their contained blood towards the heart even when a pressure of 1,000 mm. of Locke's solution is applied on the thigh above by means of a sphygmomanometer cuff. Baylis, Deuchar and I recorded the rise in the tissue pressure in the human soleus muscle on a far from maximal effort, and found it to exceed 750 mm. of Locke's solution. Abel's assumption that no pressure gradient can ordinarily be created that could propel fluid from peripheral muscular structures to the central nervous system is thus unfounded. Everyone while undertaking even the mild exercise of walking is producing such a gradient many times every minute.

After having dissented from him so often, it is gratifying to find agreement with Abel in his disbelief in Meyer and Ransom's thesis that the axis cylinders provide an intracellular conduit for this toxin. Like him, we can find no evidence for any fluid current in the axoplasm of these slender filaments, and it could only be by some mass movement of protoplasm that transport could be effected. Diffusion alone can certainly be excluded—experiments such as those of Elek (1949) on toxins in agar gels show clearly that not even under favourable conditions could diffusion carry the toxin sufficiently far in

the time interval that elapses between inoculation and the onset of spasticity. The most direct evidence that excludes axonal carriage is that obtained in some experiments made by Baylis, Mackintosh, Morgan and myself (1952) with a form of nerve sclerosis which leaves most or all of the motor fibres still functional (*see* Tables IV and V). When toxin was injected into the calf muscles distal to this

TABLE IV.—LOCAL TETANUS FOLLOWING INOCULATION OF TETANUS TOXIN INTO THE LEFT CALF MUSCLES IN NORMAL CONTROL RABBITS AND IN RABBITS WITH SCLEROSIS OF THE LEFT SCIATIC NERVE TRUNK (*From* Baylis *et al.*, 1952, with permission)

Rabbit number	Duration of sclerosis (days)	Condition of limb	Toxin (μg.)	Severity of local tetanus*	Onset of tetanus (hours)
		Control group			
31	—	Normal	15	±	120
30	—	,,	25	+++	40
32	—	,,	30	+++	72
33	—	,,	30	+	96
34	—	,,	30	+++	72
35	—	,,	50	+++	40
36	—	,,	50	+++	70
45	—	,,	75	+++	46
47	—	,,	100	+++	46
		Sciatic sclerosis group			
23	21	Toe weakness +	20	None	—
24	21	Normal	20	,,	—
22	32	,,	30	,,	—
25	32	,,	30	,,	—
27	33	,,	30	,,	—
38	20	,,	75	,,	—
39	21	,,	100	,,	—
40	15	,,	100	,,	—
42	15	Toe weakness ++	100	,,	—
43	15	Normal	100	,,	—

*+ signifies hip extension and abduction: moderate plantar flexion at ankle.
+++ signifies hip fully flexed: knee fully extended: ankle fully plantar flexed.

TABLE V.—THE EFFECT OF AN INJECTION OF TETANUS TOXIN HIGH IN THE LEFT SCIATIC NERVE IN RABBITS WHOSE LEFT SCIATIC NERVES HAD BEEN PREVIOUSLY SCLEROSED AND WHICH HAD FAILED TO DEVELOP LOCAL TETANUS AFTER AN INJECTION OF TOXIN INTO THE LEFT GASTROCNEMIUS MUSCLE GROUP (*From* Baylis *et al.*, 1952, with permission)

Rabbit number	Duration of sclerosis (days)	Condition of left hind leg before intraneural injection of toxin	Toxin (μg.)	Severity of local tetanus after the intrasciatic injection of toxin*	Onset of tetanus (hours)
38	30	Normal	40	+++	36
40	30	,,	40	+++	44
42	21	Weakness of toe extensors ++	40	+++	24
43	21	Normal	40	+++	32

*+++ signifies hip fully flexed: knee fully extended: ankle fully plantar flexed.

sclerosis, no local tetanus followed, but when it was subsequently inoculated directly into the nerve trunk proximal to the sclerosis, the limb became typically spastic. In my view, this precludes the possibility that the toxin can ascend within the axoplasm of the motor fibres.

The Pathogenesis of Local Tetanus

It is fitting that I should end this short review of local tetanus with a profession of my own belief in its pathogenesis. Tetanus is an intoxication that is highly distinctive in two respects: it is caused by a toxin whose lethal power is almost unique and it is restricted (apart from the cholinergic nerve endings in the iris described by Ambache, Morgan and myself, 1948*a* and *b*) to structures in the central nervous system. These distinctive properties of the toxin render it, I believe, quite the most

delicate indicator that we yet possess for demonstrating the transport of materials along motor nerve trunks. For reasons which I have already given, I cannot accept the view that this centripetal movement takes place within axons; instead, I believe that it is conveyed by tissue fluid currents in the spaces between the nerve fibres themselves. Such a directed flow can only take place as a result of a pressure gradient from periphery to centre, and this I think arises from the elevation of tissue fluid pressure now known to occur in the interior of a muscle on contraction. Since no comparable rise is known to take place under ordinary circumstances in subcutaneous tissues, no parallel directed movement is recognizable in cutaneous nerves—an inference in accord with the common experience of Meyer and Ransom (1903), Zupnik (1905), Sawamura (1909) and others, that local tetanus does not follow the injection of the toxin into structures innervated solely by sensory nerve fibres. Local tetanus, possibly succeeded by ascending generalized tetanus, can therefore be expected to develop when a depot of toxin is present inside a voluntary muscle mass either as a result of experimental inoculation or of local formation by infecting clostridia. Descending tetanus, on the other hand, appears when the great bulk of the toxin is located in structures other than voluntary muscle and becomes distributed to other parts of the body, and eventually to the cerebrospinal axis, by circulating blood and lymph.

"*Hodogenesis*" *and Neurotropic Viruses*

With some diffidence, I now turn to consider, from a similar functional standpoint, the kindred though more difficult questions raised by the distinctive behaviour of those viruses whose main arena of action is the central nervous system. The term "hodogenesis" was coined thirty years ago by Marinesco to provide a single useful descriptive word to cover the mounting number of instances in which it had become apparent that the particular segment of the cerebrospinal axis at which a noxious agent, such as a neurotropic virus, gains access, often corresponds with the anatomical pathway provided by the nerve trunk that connects it with the primary portal of entry. By implication, the assumption was tacitly made that the nerve trunk itself constituted the guiding conduit for the carriage of the material agent concerned. The onset of local tetanus in muscles round a wound infected with *Cl. tetani* exemplifies hodogenesis in the broader sense of Marinesco's term. In experimental studies on neurotropic viruses, such as those of rabies, pseudo-rabies, poliomyelitis and herpes, the concept of hodogenesis is particularly well illustrated. In these latter instances, moreover, there can be no doubt about the centripetal passage of the agent itself, for both the recoverability of the virus from the regional segments and the striking histological signs of local injury provide an irrefutable demonstration that the virus itself is carried to the damaged portion of the central nervous system. Because the concepts of hodogenesis and nerve trunk transportation seem to have much in common both for local tetanus and for infections with neurotropic viruses, and since investigators have traversed much the same ground in their search for some physiological mechanism that might account for them all, I shall briefly consider what light they may throw on one another.

Axonal carriage of viruses.—Ever since Goodpasture and Teague (1923) in the United States and Marinesco and Draganesco (1923) in Rumania published almost simultaneously thirty years ago their analyses of the herpes encephalitis of rabbits that follows inoculation of a scarified cornea, the mode of transport of the virus from the eye to the brain has been in dispute. Both groups of investigators agreed that it followed a neural pathway to the medulla oblongata, but whereas Goodpasture and Teague thought that it probably ascended through the axons of the sensory division of the trigeminal nerve, Marinesco and Draganesco considered that it was more likely that it was carried centripetally along the spaces between the fibres of this nerve trunk. The same problem and dilemma thus emerged for the neurotropic viruses as had previously posed themselves to the student of local tetanus.

In sustaining his belief, Goodpasture (1925) placed much weight on some observations he made during a histological study of the early lesions in the brain-stem of rabbits that followed an inoculation of the masseter muscle with herpes virus. Seeking for signs of injury as indicators of the route taken by the virus, he could find little damage in the motor division of the trigeminal nerve, in the meninges round the site of its emergence from the brain-stem, or in the immediately subjacent neuroglial cells, although the cells that composed all these structures were vulnerable to its action. At the stage of the infection when these portions of the nervous pathway appeared uninjured, however, the neurons that composed the trigeminal motor nucleus showed signs of serious damage. The essence of Goodpasture's argument was that the absence of evidence of injury to the susceptible meningeal and neuroglial cells could best be interpreted by assuming that the virus had been carried past them—canalized, as it were, in the axoplasm of the entering nerve fibres. Had the virus arrived by way of the tissue spaces of the nerve trunk, to be released in the interstices of the glia just beneath the meninges he would have expected that the near-by glial and meningeal cells would have incurred the brunt of the attack and have shown signs of damage accordingly.

Apart from Goodpasture's work on herpes encephalitis, the firmest support for the theory of intra-axonal carriage has been provided by Weston Hurst (1930, 1936). In an illuminating study on the spread of poliomyelitis virus in the nervous system of monkeys that followed inoculation of the left sciatic nerve trunk, he could trace its spread from the nerve to the lumbar cord and soon afterwards to the leg area of the right motor cortex of the cerebrum. Thus, the decussation of the descending

pyramidal motor tracts in the brain-stem seemed to be associated with a corresponding crossing in the path taken by the ascending virus—a correlation whose attractiveness for the theory it would be impossible to overlook.

Although the theory of axonal carriage has been advanced persuasively by its supporters, there seem to be substantial reasons standing in the way of its acceptance. Firstly, it has been found that the poliomyelitis virus can spread from the lumbar to the cervical enlargement even after a transection in the dorsal region that not only widely separates the two parts of the cord but also effectively obliterates the near-by subarachnoid space. Howe and Bodian (1942, p. 84) also found that even the additional cutting of the paravertebral sympathetic nerve chains at the same time as the cord failed to prevent the spread upwards of the virus, and in defence of the axonal theory they were constrained to suggest that in such monkeys it may pass first to the wall of the gut where in Meissner's and Auerbach's plexuses it can come into contact with pre-ganglionic fibres of the vagus nerve and thence ascend to the brain. The belief that this virus can thread such a maze in the short period of a few days seems to me to place too great a strain upon credulity, and urges us to seek for some simpler explanation. Secondly, from observations of Howe and Bodian (1942, p. 18) on the centripetal movement of poliomyelitis virus in monkeys' sciatic nerves, it would seem that it can ascend them at a rate of between 2 and 3 mm. an hour, and the hypothesis of Weston Hurst for the movement of this virus in the pyramidal tracts would lead to much the same conclusion. What force could propel these virus particles for a distance some ten or more times their own diameter every second through a matrix that is at least viscous and may be semi-solid has not, as far as I know, yet been suggested. Since it seems inadmissible to invoke any concept that involves a mass movement of the axoplasm within the fibre, the theory must, it would seem, have recourse to some form of creeping canalized replication of the virus, perhaps in the form of still smaller specific elements, along the interior of the axon. Lastly, it seems difficult to believe that a virus which is known to be so destructive to nerve cells as that of poliomyelitis can thrive and spread inside an axon without in some way impairing its ability to conduct nervous impulses. Yet in Weston Hurst's experiments, the monkeys whose sciatic nerves had been inoculated with this virus showed no paralysis of that leg until the virus had become recognizable in the lumbar cord. It would seem that a neurophysiological study of the ability of infected nerve trunks to conduct nervous impulses, on the lines of that made by O'Leary and his colleagues (1932), might throw further light on this aspect of the problem.

Nerve tissue spaces as pathways for neurotropic viruses.—This rival theory of Marinesco and Draganesco (1923) was also chiefly based on a careful histological exploration of the intervening nervous tract from periphery to brain in rabbits whose corneas or masseter muscles had been inoculated with herpes virus. After an infection of the eye, they could trace a chain of inflammatory foci by way of the ciliary and gasserian ganglia to the brain-stem itself (Fig. 3). From the apparently interstitial situation of these lesions, they inferred that the virus had spread along this path by way of tissue spaces. In 1932, they returned to the problem, and repeated Goodpasture's experiments on masseter inoculations—again with discordant results. In their rabbits, the gasserian ganglion was always infiltrated with inflammatory cells, and though they sought specifically for evidence of damage to the trigeminal motor nucleus, they found none. Instead, the trail of injury showed that after it had

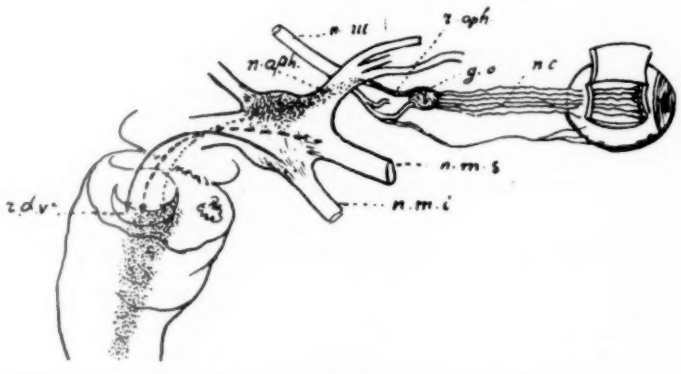


FIG. 3.—Diagram showing the route by which the herpes virus travels from the cornea along the ciliary nerves (*nc*), then from the ciliary ganglion (*go*) and its sensory root (*r. oph*) to the ophthalmic nerve (*n. oph*) and the outer part of the gasserian ganglion. In the medulla oblongata a focus of degeneration is seen, in the descending division of the trigeminal nucleus. (*From* Marinesco and Draganesco, 1923, with permission.)

reached the gasserian ganglion, and irrespectively of whether it had come from cornea or masseter, the virus progressed centrally along both the sensory and motor components of the trigeminal nerve. Thus infections with this virus in peripheral structures supplied by branches of either the sensory or motor division of this nerve could lead subsequently to the involvement of both the motor and sensory centres in the brain-stem. They could find no evidence of the specificity of route and destination described by Goodpasture and which he regarded as indicative of a directed axonal carriage of the herpes virus.

In retrospect, it is difficult to account for the contrary conclusions as to the mechanism of hodogenesis that were reached by two groups of investigators who by a strange coincidence were working simultaneously and independently with the same virus on the same animal preparation. Doerr (1939, p. 733), in his extensive review of hodogenesis, tried to resolve the disagreement by relating the differing findings firstly to the different strains of virus used, and, secondly, to the fact that Marinesco and Draganesco examined their animals at a later stage of the infection, by which time the virus might have more fully disclosed its pathogenic potentialities. The first suggestion can no longer be tested, but the second, and more likely one, is still open to further experiment and might well repay a re-opening of the problem.

Marinesco's belief that neurotropic herpes virus passes centripetally along tissue spaces in nerves has, I think, more to commend it than the intra-axonal theory, though the evidence in its favour, recently further supported by Field (1952), is still only circumstantial. It receives support from the occurrence of typical inclusion bodies in Schwann cells along the course of the nerves in which the virus is known to be ascending. Weston Hurst (1933) found a chain of such infected cells along much, though not the entire length, of the sciatic trunks of rabbits that had been inoculated distally with pseudo-rabies virus. From this he inferred that this virus did move along tissue spaces, though more slowly than up the axons. Similarly, Goodpasture (1925) saw herpes inclusion bodies in Schwann cells in the motor trigeminal nerve after inoculation of the masseter muscle, but he explained this finding differently by supposing that at various points along their course the axon and myelin sheath of the conveying fibres had been damaged to a degree that permitted the local escape of the virus. A further consideration that favours Marinesco's view is that the calculated rates of ascent of viruses are more comprehensible on the assumption of passive carriage by tissue fluid currents in the spaces in the trunk. When the interval between the injection of the virus distally in a limb and the onset of recognizable central sequelæ is divided, as Doerr has pointed out, into three periods of absorption, transmission and central action respectively, the time taken for transmission for viruses comes sensibly nearer to that found for tetanus toxin.

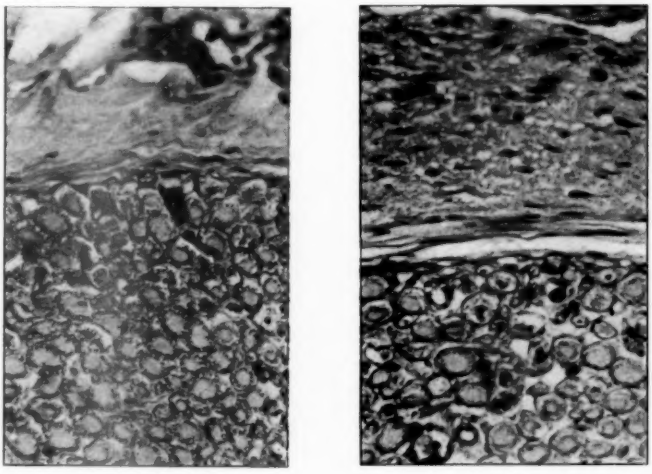
To set against these favourable considerations, however, are certain experimental findings for whose explanation the theory is less satisfactory. Firstly, there is the observation that the neurotropic herpes virus at least, and perhaps other such viruses, too, can move centripetally in both motor and sensory nerve trunks. Here, parallelism with the hodogenesis of local tetanus seems less complete, for since the work of Zupnik (1905) and of Sawamura (1909) many years ago, it has been recognized that injections of this toxin into sites innervated solely by sensory nerves do not give rise to local tetanus but to that form known as descending tetanus which is typical of a blood stream spread. Yet not only did Goodpasture and Marinesco and their colleagues find that herpes virus could spread along the sensory nerves of the cornea, but Rose and Walthard (1926) also observed a centripetal carriage from infections in the skin of the hind-feet of guinea-pigs. Five to ten days after inoculation, such animals became paralysed, and the spinal cords later showed a typical myelitis. Secondly, interference with the patency of the tissue spaces of a nerve trunk by chemical sclerosis, a procedure which, as I have already pointed out, is effective in preventing local tetanus after a distal inoculation of the toxin, seems to present no such obstacle to the ascent of a neurotropic strain of herpes virus. In some experiments which Wright, Morgan and I made, sclerosis not only raised no barrier to the ascent of a neurotropic (Brussels) strain of herpes virus, but seemed even to have somewhat hastened the onset of the subsequent myelitis (Table VI). Inferences from this observation must be drawn cautiously,

TABLE VI.—DEATHS FOLLOWING INJECTIONS OF HERPES VIRUS INTO SCIATIC NERVES OF CONTROL AND SCLEROSED RABBITS

	Days after injection			
	7	9	11	13
Control group (12)	0	3	4	5
Sclerosed group (12)	0	7	9	10

(Wright, E. A., Morgan, R. S., and Wright, G. Payling, unpublished observations.)

however, for this virus is not exclusively neurotropic, and the newly proliferated connective tissue elements in the zone of sclerosis (Fig. 4) may have assisted the infection by promoting the local multiplication of the virus.



(*a*) (*b*)

FIG. 4.—Sections through (*a*) normal and (*b*) sclerosed sciatic nerves showing granulation tissue annulus and increased cellularity of the endoneurium in the latter. (× 290.)

The mechanism responsible for hodogenesis.—I have now reviewed very briefly some of the problems presented by Marinesco's concept of hodogenesis. Search for the mechanisms responsible for this phenomenon has long exercised the ingenuity of students of infections and intoxications of the central nervous system, and seems likely to engage their interest for many years to come. How far the simpler issues involved in the pathogenesis of local tetanus throw light on the transportation of the neurotropic viruses is controversial, but studies with this toxin have at least provided some positive information that bears on the more complex problem. It has shown with a high degree of probability that small amounts of material can be carried centripetally along motor nerve trunks—not in the axons but in the tissue spaces—and if a directed current of fluid can bear the toxin along these channels, it would seem a reasonable economy in hypothesis to assume that virus too can be carried in the same way. It seems unlikely that a mechanism which is effective for the conveyance of tetanus toxin can be wholly inoperative for virus. For although the quantity of this toxin that is needed to cause a regional intoxication in the spinal cord is minutely small, the amount of a replicating virus required to establish an infection there might well be much smaller. To me, at any rate, it seems that the physiological mechanism of gross oscillations of tissue fluid pressure in certain peripheral structures which probably effects the one, might readily suffice for the other.

Conclusion

I have reviewed very briefly and with many important omissions a problem in Pathology which has given rise to much speculation and controversy amongst students of tetanus and the neurotropic viruses. Although I realize that many of the points raised may be more of technical than of general interest, I have chosen to speak of the role of nerve trunks in these infections largely because it illustrates particularly well how the search for a coherent explanation in almost any pathological problem requires the integration of material gathered from the whole general body of the medical sciences. Rifts are appearing in the fabric of scientific medicine and show signs of widening yearly. The growing content of each science is placing a severe strain on the powers of its followers to keep pace with its progress. But it seems to me that there is less danger to Pathology from this pressure of increasing knowledge than from the fact that the links which connect it with its kindred sciences, and particularly with Physiology, are becoming more tenuous every year. Each science, and Pathology—too often synonymous with nineteenth century morphology—more than most, is suffering from an isolation which is largely brought about by our modern tendency to segregate ourselves in specialist societies. We should not, I am convinced, accept any such narrow connotation for the word

"Pathology"—we should rather interpret it as did Fernel, when just four hundred years ago he gave the name to our science, as including any aspect of medical science that renders the processes of disease more comprehensible. I feel sure that one of the most useful services that this Section can render both to Pathology itself and to Medicine in general is to serve as a forum for speakers with widely different but complementary scientific interests. If it follows this policy, it can do more than any other Section of this Society to bring together those who work in separated academic and applied fields in Medicine, and thus lessen the danger of an insularity of outlook and neglect of the increasingly powerful experimental methods becoming available yearly which must inevitably react to the detriment of progress in Pathology.

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Proceedings of the Royal Society of Medicine Vol. 46 331

Section of Physical Medicine

President—DONALD WILSON, M.B., M.R.C.P.

[*December* 10, 1952]

DISCUSSION ON THE PRESENT POSITION OF SHORT-WAVE DIATHERMY AND ULTRASONICS

Dr. Bryan O. Scott (Department of Physical Medicine, Radcliffe Infirmary, Oxford):

Short-wave diathermy is generally regarded as a powerful therapeutic agent. However, an extensive search of the literature has not revealed any report of controlled clinical investigation into its efficacy. In fact, the reputation of short-wave seems to derive from its known ability to produce deep heating and the impression of experienced workers with this agent. That heat is beneficial in certain pathological conditions is beyond dispute and the distribution of such heat in tissues exposed to a short-wave field has been shown in numerous experiments *in vitro* and *in vivo*.

The use of short-wave as a control (or as a comparison) for other methods of treatment is helpful, but it limits the estimation of the effectiveness of those methods to an arbitrary standard. Indeed, unless it is assumed that the methods to be compared achieve their therapeutic results by the same mechanism, direct comparisons are of little value. For this reason the title of this discussion is not meant to imply a comparison between short-wave diathermy and ultrasonic therapy. Neither has been the subject of a controlled investigation and the latter probably has a use in therapeutics apart from that as a source of heat.

Production.—Short-wave diathermy is the name given to therapeutic heating by high-frequency currents oscillating at between 10–100 megacycles per second. Such currents are produced by an oscillator circuit of the required frequency, the energy losses being made good, in modern machines, with the aid of thermionic valves. The energy can be transferred to a patient either by means of condenser electrodes or by induction cable. In either case the oscillator circuit is coupled to another circuit of the same constants, of which the patient or the induction cable is an integral part.

EFFECTS

(*a*) *Heating.*—The main effect of short-wave diathermy is heating in depth. The physiological results of this heating include hyperæmia, hyperlymphia and hypersecretion (Kovacs, 1949). This statement requires qualification because there have been recorded instances of vasoconstriction occurring following short-wave therapy (Kottke *et al.*, 1949, and Flax *et al.*, 1949). Further, the vasodilation produced by short-wave is not maximal since a further increase can be produced in patients by the subsequent administration of tetra-ethyl ammonium salts (Bierman *et al.*, 1950).

(*b*) *Effects on central nervous system.*—Claims have been made that short-wave diathermy exerts a sedative effect on irritative conditions of sensory nerves (Audiat, 1932). Krusen and Brunner (1940) stated that the chronaxie of muscle was increased during exposure to short-wave diathermy. However, Hill and Taylor (1937), after an extensive trial, were unable to demonstrate any change which could not be attributed to the heating effect.

(*c*) *Effects on bacteria.*—Heat produced by either ultra-high-frequency energy (or any other method) can destroy all bacteria provided it exceeds the critical temperature of the particular bacteria. Nyrop (1946) claimed that "athermic" diathermy destroyed certain organisms. In his experiments he used a pulsed field to minimize heating, thus allowing time for the dissipation of heat. However, attempts to repeat these experiments have been unsuccessful. Modern medicine relies on the use of the antibiotics in the tissues; the bacteriocidal effect of short-wave being of historical interest only.

(*d*) *Effects on the blood.*—Liebesny (1938) demonstrated that pearl chains were formed in fat emulsions and in blood when subjected to a high-frequency field. He made no comments as to the therapeutic advantage of this fact. It seems, therefore, that this effect also must be of academic interest only.

It may be concluded that the therapeutic effects of short-wave diathermy are due to deep heating and that it has no specific effect in these circumstances.

MEASUREMENT

Until recently there has been difficulty in measuring the power input of high-frequency energy into a patient. This difficulty has been largely overcome by the development, at St. Thomas's Hospital, of a self-tuning short-wave generator with a wattmeter. By means of such an apparatus the power absorbed by a patient can now be measured in watts. If the physical properties of all patients and their reaction to treatment were identical, it should now be possible to obtain accurate dosimetry with this therapy. The load absorption with short-wave diathermy is to some extent controlled by variable

factors obtaining in the condenser, of which the patient forms a part. In the case of ultrasonics, the transducer head is placed on the skin and the energy transferred to the patient is directly proportional to the output of the machine, irrespective of the patient's reactance. With short-wave, however, this is not always possible, as the losses which occur in the patient's condenser are variable. These losses vary with power output, spacing, the physical properties of objects in the field and their position.

It remains to be proven whether measurement of dosage in short-wave therapy will be of practical value. A generator has been produced which measures the power input accurately and delivers a constant power, but the variables in the tissues and in the application may well prove to be too great for accurate dosimetry to be achieved.

Application

The application of short-wave diathermy to human tissues appears at first sight to be a simple matter, but in fact this is not correct. The *correct* application of short-wave energy is the very basis of successful treatment. There are three requirements for successful treatment:

First: The pathology must be correctly diagnosed.

Second: It must be decided whether or not the application of deep heat will be advantageous, and, if so, what structures are to be heated.

Third: Short-wave diathermy must be applied by those who have a knowledge not only of high-frequency currents and electric fields, but also the capabilities of the generator they employ.

The need for accurate diagnosis and competent operators is obvious. When considering the structures to be heated their physical properties and spacial distribution must be remembered. If condenser electrodes are used, fat is heated more than muscle, due to the relation between the power factor, dielectric constant and the square of the field strength in these tissues (Scott, 1952).

If inductothermy is used, the heating depends mainly upon eddy currents. As these flow more readily in muscle owing to its high fluid content, muscle obtains the greatest heating. There is, in addition, some heating due to the dipolar effect as with condenser electrodes.

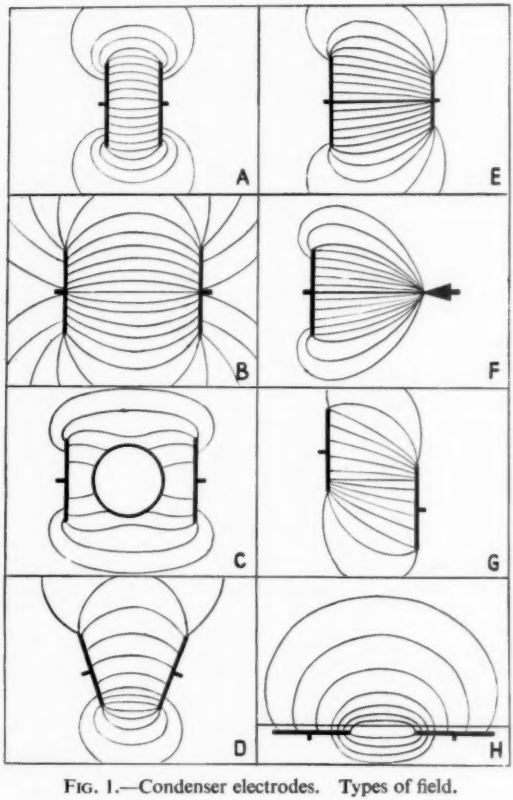

FIG. 1.—Condenser electrodes. Types of field.

Factors to be Considered in the Technique of Application of Short-wave Diathermy

(*a*) *Output of machine*.—The output of the generator must be adequate. The treatment of patients with a generator whose output has fallen is virtually useless. It is advantageous, therefore, to test apparatus by phantom loads from time to time. For instance, a generator may be tested and found to have a low output; subsequent enquiry may lead to the discovery of defects in the valve or in the coupling; I remember on one occasion testing an apparatus in regular use, which was, I am told, efficient in use, which had a maximum output of only 9 watts. This was due to the coupling being too tight. Rectification of this fault resulted in a normal output.

(*b*) *Tuning*.—Accurate tuning of the resonator circuit is essential and this must be maintained throughout treatment. Anything which has reactance (C or L) will disturb the circuit constants and may detune the resonator circuit. This occurs particularly when the resonator has a sharp tuning (or response) curve. An efficient apparatus will have good selectivity, the circuit having small resistance. A generator which has a flat tuning curve will probably be over-damped in the resonator circuit which causes a lower voltage drop across the patient, resulting in a weaker electric field

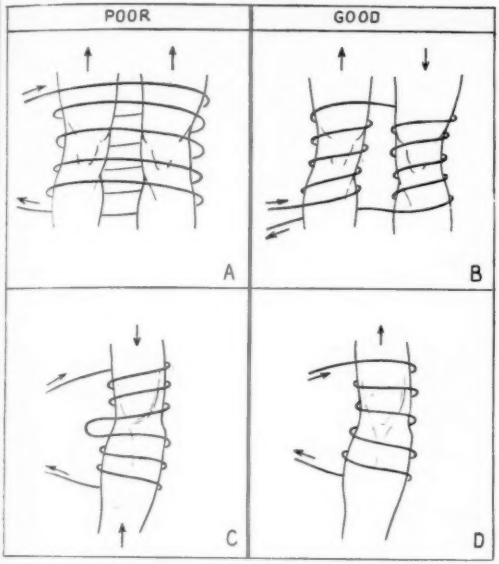

FIG. 2.—Methods of winding coil.

(*c*) *Position of electrodes.*—One of the better methods of deciding the position of the electrodes is to visualize the shape of the field and adjust the electrodes accordingly. In this way it is easier to concentrate the heating in the desired situation.

Fig. 1 shows by simplified field diagrams the type of fields which can be expected from various positions of the electrodes, the density of the field being related to the heating pattern. The insertion of a conductive body in the field will probably cause an indrawing of the field (Scott, 1953).

Distortion of the field can also occur when an object is close to the electrodes or lines. An obvious cause of energy loss, which is sometimes forgotten, is the presence of the operator too close to the patient's circuit.

When applying the inductothermy cable it should be wound to obtain maximum inductance and thus the maximum formation of eddy currents. Should it be necessary to have two coils these can be arranged so that they are "series aiding" and not "series opposing" (*see* Fig. 2). The power input into phantoms when the cable is wound as in B is approximately 60% more than when wound as in A. The power input in D is approximately 70% better than in C. B is wound "series aiding". C is wound "series opposing".

(*d*) *Spacing of electrodes.*—The spacing of the electrodes is a major factor controlling the input into the patient. Deep spacing alone does not produce deep heating. An increase of the spacing does two things:

First: It decreases the flux density of the field at all points. This decreases the field strength both in the skin and also in the deep tissues. Such a decrease is not constant, it is greater in the skin than at the centre, i.e. a more uniform field is produced. It follows that the ratio of the field strength in the centre to that in the skin is much greater with close spacing. Thus deep spacing only causes *relatively* more heat in the deep structures.

Fig. 3 shows the power absorption on the axial line of the field which takes place with ¼ in. and 1 in.

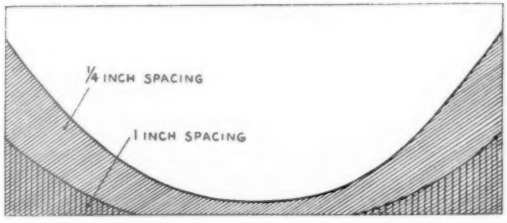

FIG. 3.—Condenser electrodes. Power absorption.

spacing. It indicates the decrement in the field strength from without inwards and that increased spacing leads to a more uniform field.

Second: An increase of the spacing decreases the power input into the patient. This decrement is very rapid. When the spacing is increased the power input into the patient falls, but a more uniform field is produced. Power can then be increased until the original intensity of skin heating is reached. This can only be achieved if the generator is sufficiently powerful to compensate for the increased absorption of the patient and the increased losses which occur at the same time. The available output of the generator may not compensate for the increase of load.

Fig. 4 shows the relation of spacing and output to power absorption in a phantom. Note that with the output constant the input depends upon the spacing and also that as the spacing is increased and

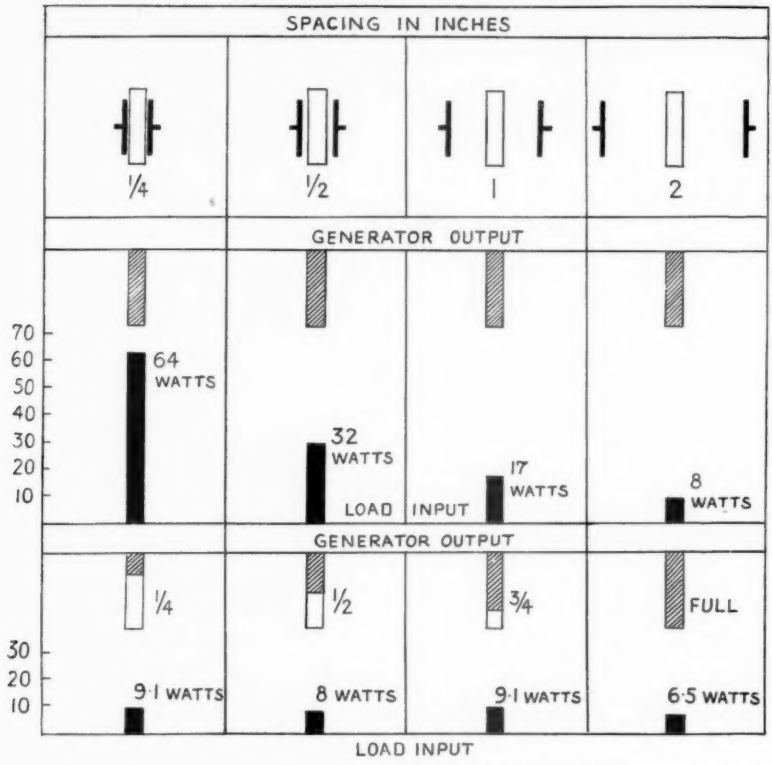

FIG. 4.—Power absorption. Relation of spacing and output.

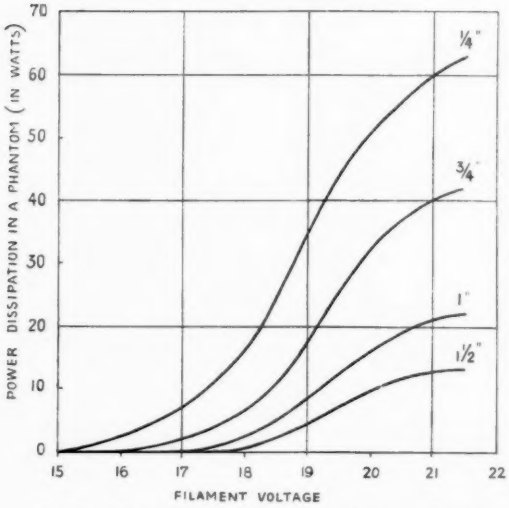

FIG. 5.—The power dissipation in a phantom plotted against the filament voltage.

generator output is increased the input remains the same. The power absorption in this case is very low and falls off at 2 in. spacing.

It follows that a decrease in the heating of deeper structures *can* occur with an increase of spacing. Suppose for example with close spacing the skin receives 8 units of heat and the centre 1 unit (a ratio of 8 : 1). With an increase of spacing this ratio may fall to 6 : 1, a relative increase in deep heat, but as a result of the fall in power reaching the patient, the skin will only be receiving about 3 units. The centre will then receive ½ unit which is less than before.

Thus the output of the generator may have to be trebled in order that the centre may receive more heat than with the original spacing. This would mean at a ratio of 6 : 1 (9 units in the skin and 1½ in the centre). The generator output has been raised to 300% to increase deep heating by only 50% in this example.

Fig. 5 shows the power dissipation in a phantom plotted against the filament vol-

tage. For example, an input of 20 watts is obtained with ¼ in. spacing with a filament voltage of 18·25 volts. If the spacing is to be increased to 1 in. the filament voltage has to be increased to 20·75 volts to maintain a 20 watt input. This means that the output of the generator has been trebled. If, however, the spacing is increased to 1½ in. then a 20 watt input cannot be obtained.

Although it is possible to produce increased heating in the centre with increase of spacing, a balance must be struck between the ratio of the field strength in the tissues on the one hand, and the power input into the load on the other. Most of the present-day machines will not allow spacing greater than 1½ in. without considerable weakening of the field. Clearly the spacing must not be deeper than can be compensated by increased output from the generator.

Uses in Treatment

Over 200 separate conditions or disease groups have been treated in the past with varying degrees of success.

Short-wave therapy is reported to have many indications and contra-indications. If we consider these reports in connexion with bone pathology it is probable that if conditions in the tissues or blood predispose to osteoporosis, short-wave is contra-indicated, but if the reverse, then short-wave will assist osteogenesis.

When deep heat will assist the physiological response to bring about a reversal of the pathological change, short-wave is indicated. If this is not so, or if the pathological process will be accelerated by deep heat, then short-wave is contra-indicated.

Uses in Diagnosis

Claims have been made by Shliephake (1950) that short-wave can assist in diagnosis. He reports that a significant increase in the white cell count after five minutes' short-wave applied to the appendix area indicates the presence of chronic appendicitis. He claims similar effects in latent cases of endocarditis and myocarditis (he accepts an increase of 2,000 or more cells per cubic millimetre as significant). The same author states that it is possible to differentiate between pituitary and pancreatic diabetes mellitus by a similar method using estimation of the blood sugar instead of blood counts.

These reports have not been supported by controlled figures. More work is therefore required to establish whether or not short-wave diathermy is a useful method in electrodiagnosis.

Summary

The production and effects of short-wave diathermy are outlined and briefly discussed.

The technique of application is indicated and some of the difficulties and pitfalls demonstrated.

The importance is shown of the correlation between the output of the generator and the correct positioning and spacing of the electrodes, in order to ensure adequate treatment.

Comment is made on the uses in treatment and diagnosis and the basic indication for short-wave therapy is suggested.

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Dr. I. H. M. Curwen (Department of Physical Medicine, St. Thomas's Hospital):

Ultrasonic energy is a form of mechanical energy which is propagated through material media as a longitudinal wave. Like the waves of audible sound, these cause alternating zones of pressure and rarefaction. The term "ultrasonic" is applied to energy of this type when the frequency of the waves is greater than 20,000 cycles/second, which is defined as the upper limit of audible sound.

Production.—For therapeutic purposes it has been found that frequencies of 800 to 3,000 kilocycles/second are required. Frequencies of this order can be produced by a transducer containing a quartz

crystal, or a plate of barium titanate stressed by a direct current. The principle is the converse of the piezo-electric effect. If an alternating electrical potential of the required frequency is applied across the crystal or oxide plate, it will vibrate at that frequency if it is of suitable thickness; the electrical energy being thus converted into mechanical energy. The crystal is closely applied to a metal plate and enclosed to form the watertight applicator or treatment-head of the apparatus.

Application.—Ultrasonic energy is partly reflected from any interface between the media in its path. Almost total reflection occurs at the interface between the treatment head and the surrounding air; it is therefore necessary to interpose a contact medium between the applicator and the body tissues during treatment. Liquid paraffin, glycerin or light ointment is used for large tissue areas and a water bath or oiled water-bag is used for irregular areas such as the hand, where direct contact with the applicator would be difficult.

Measurement

The output of the apparatus indicates the intensity received by the tissues, since the loss of energy between the transducer and the patient's skin is negligible. A meter in the electrical oscillator circuit may therefore be calibrated to indicate the intensities used in treatment. A separate pressure meter may also be used to measure the actual energy output from the transducer, but this probably has little advantage over the previous type. Intensity is measured in watts/sq.cm. Energy passes into the tissues as a beam, but it must be realized that the maximal intensity is in the centre of this beam. Energy is dissipated as heat throughout the path of the beam. The body tissues are not homogeneous, so that partial reflection takes place at the interfaces between the tissue planes and further absorption of energy occurs in these areas. Pohlman (1948) has calculated that half the intensity is lost at a depth of about 3·5 cm. in living tissues. The meter therefore gives an indication of intensity applied to the surface, but no indication of the intensity in depth. Thus, although accurate measurement is easily possible, accurate dosimetry with regard to deep tissues is not. As in the case of short-wave diathermy, measurement of intensity can be used only as a standard of comparison. The range of intensities usually used in treatment lies between 0·5 and 3 watts/sq. cm. If the applicator is stationary upon the tissues, heating is maximal and only low intensities are tolerated by the patient; in this case also, standing waves may be set up, which will alter the mechanical effect upon the tissues. For these reasons the transducer is usually moved slowly over the part under treatment. If the intensity is steadily increased, a point is reached where the patient feels pain due to deep heating. Heating is especially marked at tissue interfaces such as the periosteum of underlying bone. The subjective pain experienced by the patient limits the intensity which can be used in practice, as thermal sensation limits the use of short-wave diathermy.

Effects

The effects of ultrasonics upon tissues have been extensively studied in isolated preparations and in the living organism. These are thermal, mechanical, chemical.

Thermal effects are similar to those of other physical agents; but they differ in that with ultrasonics the heating which occurs in muscle is twice that in fat and localized intense heating takes place at tissue interfaces. It has been postulated that this localized heating is due to distortion of the wave-form which occurs on reflection in the same way as light is partially polarized on reflection from a mirror.

It is possible to produce gross damaging effects upon tissue in the living organism by the use of high intensities of ultrasonic energy (Anderson *et al.*, 1951; Fry and Wulff, 1950; Council, &c., 1952). Pathological changes produced are typical of burning, with splitting of tissues by the mechanical effect. Overheating of tissues is avoided during treatment by moving the applicator slowly over the part and limiting the intensity used so that no pain is experienced by the patient. With the moving treatment head, the rise of temperature within the tissues is seldom greater than 3° C.; for this reason thermal effects are thought to be of less importance in ultrasonic therapy than in other forms of physical treatment.

Mechanical effects.—The wavelength of the ultrasonic beam in the tissues at 800 kc./sec. is about 2 mm. Particles in the beam are moved back and forth over very small distances at an acceleration 100,000 times that of gravity. Considerable forces are applied, so that, at an intensity of 5 watts/sq. cm. the pressure difference between the zones of pressure and rarefaction is about 8 kg./sq. cm. or 117 lb./sq. in. These forces are acting across 1 mm. of tissue (Schliephake, 1950). Total disruption of small organisms such as paramecium can be observed in water through which an ultrasonic beam is passed (Bosco, 1949). Muscle fibre preparations show splitting of the fibres, probably due to the phenomenon of cavitation in which gas bubbles appear instantaneously in the zones of pressure reduction (Garay and Gerendas, 1949). These destructive phenomena do not occur at therapeutic intensities and would represent gross overdosage by therapeutic standards.

During exposure there is a stirring effect within the cells causing an increase in the gradient of ion concentration near the membranes and these are set in rapid oscillation producing an acceleration of

fluid exchange with an apparent increase in permeability of all cell membranes (Schwan and Carstensen, 1952). This promotes local tissue metabolism which is further increased by the thermal effect. The mechanical effect is said to account for the different therapeutic results claimed for ultrasonics when compared to those of purely thermal agents. It probably accounts for the softening of areas of fibrosis and scar tissue which is seen clinically and also for an increased rate of absorption of tissue exudates and effusions of blood.

Chemical effects.—Ultrasonic energy has been shown to be capable of splitting long-chain molecules; thus sucrose may be split into monosaccharides (Bosco, 1949). It is also able to increase the speed of oxidation and it is possible that this occurs at therapeutic intensities.

Other specific effects claimed for ultrasonics include the disruption of protein with effects similar to those of other non-specific protein shock therapy and the possibility of driving drugs into the tissues as in iontophoresis. It has many non-medical applications in the promotion of physical and chemical changes from the mixing of paint to the maturing of whisky.

Dangers

It is obvious that precaution must be taken in the therapeutic use of this potentially destructive agent. The treatment of many thousands of cases on the Continent and in America has, however, proved that its use is safe in the hands of a competent operator. The dangers are probably no more important than those incurred in the use of short-wave diathermy.

The first criterion of safe treatment is that it should be painless, so denervated tissues should be treated with caution. Tumour tissue of certain types can be destroyed by ultrasonic energy, but it may cause rapid metastasis, so it was decided at the International Congress on Ultrasonics held in Rome in 1950 that tumours should not be exposed to ultrasonics except experimentally for purposes of research. Acute infections should be treated cautiously, for spread of infection may occur; on the other hand, many workers have reported the successful treatment of boils and carbuncles. Certain special tissues have also been found to be subject to damage. The brain, the eye, ovaries and testes, the gravid uterus, epiphyses of growing bones and the cervical ganglia in cases of myocardial damage, comprise the usual list. Here again, the dangers are probably relative. Many of these tissues have been treated by experienced workers without damage, although in some cases special techniques were employed; thus thousands of children have been treated without damage to bone growth. Pulsed energy has been used on the brains of experimental animals with no destructive effects and the cornea has been treated for opacities without causing separation of the retina.

A vast and incongruous list of conditions have been treated by ultrasonics. Many hundreds of articles have appeared in the literature since Dognon *et al.* (1937) reported on the biological effects of ultrasonics and Pohlman and his co-workers (1939) published their first paper on the therapeutic use of this new agent. An excellent critical survey of the significant literature was published by Nelson *et al.* in 1950. Research work of great value has been performed on the subject, but the clinical studies have frequently lacked a critical approach. Few physical agents have been as thoroughly investigated in the laboratory as ultrasonics, yet, with the passage of time, they have found their rightful place in the range of useful therapeutics.

In physical medicine today we demand that figures should be produced to support every claim of therapeutic results depending on clinical observation. It is, however, important to realize that in physical medicine results frequently depend upon the subjective relief of a painful condition reported by a patient. Controlled clinical trials have, however, been reported by Aldes at the first International Congress of Physical Medicine, and by Friedland *et al.* (1952).

Material and Method of Treatment

During the last two years, about 150 cases have been treated at St. Thomas's Hospital out of which 120 cases are considered.

These cases were treated on two generators of different types. Treatments were given by a small group of physiotherapists who were carefully instructed in the technique. Intensities used varied between 0·5 and 3 watts/sq. cm. and were given for periods up to fifteen minutes at each attendance. The moving treatment head was used whenever this was possible. Contact with the tissues was obtained by the use of liquid paraffin or a water bath. Local treatments only were used. No attempt was made to influence the local condition by treating the area of the spinal segment or autonomic ganglia related to the part in which the lesion was situated; it was considered that if local effects could only be produced in that way then the injection of nerve roots or ganglia with local anæsthetic would prove as efficient as ultrasonic therapy.

The results are taken from the ordinary departmental case notes. Wherever possible objective signs have been assessed.

Results

Table I indicates the critical assessment of the results obtained in 104 cases out of the 120 case notes considered. These cases were selected as giving reasonable grounds for comparison with similar cases treated by conventional physical methods. Cases were considered to be "significantly improved" only when the results of treatment appeared to indicate a definite advantage in the use of ultrasonic therapy over the control series. Many of the cases treated by ultrasonics showed improvement directly comparable to that of the control series, but for the sake of simplicity no indication of these cases has been given.

TABLE I

Diagnosis	No. of cases	No. significantly improved
Lesions of tendons and allied structures—		
Lesions of rotator cuff and supraspinatus strain	6	0
Tennis elbow	12	0
Lesions of tendon sheaths and bursæ	4	3
Lesions of joints—		
Osteoarthritis	6	0
Residual pain of lumbar joint derangement	5	0
Coccydynia	2	0
Chronic joint strain	9	3
Osteochondritis of spine	3	1
Ankylosing spondylitis	11	6
Soft-tissue lesions—		
Causalgia and painful neuromata	10	0
Dermatomyositis	2	0
Localized scleroderma	2	0
Acne and folliculitis	6	1
Indolent gravitational ulcers	3	0
Lymphatic œdema	3	1
Dupuytren's contracture	8	3
Contracted and adherent scars	12	10

Discussion

Certain interesting features are apparent in this small and diverse series. The results of treatment in ankylosing spondylitis are interesting. The literature reports good results in the treatment of this condition, and, although there is no suggestion that any form of local treatment can alter the course of the disease, ultrasonics may prove a useful alternative to high-voltage radiotherapy in the alleviation of pain in this condition. Its use is certainly worthy of trial in a case of recurrent pain where a skin-tolerance dose of X-rays has already been given and in the rare case of the condition affecting the young female.

The results in the treatment of local contracted scar-tissue are noteworthy. It would appear that in this condition the mechanical effect of ultrasonics, by increasing permeability and thus causing softening, may be of considerable value when combined with local active and passive stretching.

In general the assessment of results confirmed Friedland's opinion that ultrasonics has a pain-relieving effect equal to the analgesic effect of thermotherapy. It has, therefore, a definite therapeutic value. There are some indications that it has properties other than those of heat in producing its effects.

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[*January* 14, 1953]

DISCUSSION ON THE ROLE OF PHYSICAL MEDICINE IN GERIATRIC PRACTICE

Lord Amulree: The role of physical medicine in geriatric practice can be divided into three parts:

(1) Restoration of function in (*a*) chronic sick patients; (*b*) acutely ill patients.

(2) Maintenance of function for as long as possible.

(3) Prevention of disabling disease.

The restoration of function to chronic sick patients.—The term "chronic sick" will, I hope, soon be as obsolete as the majority of the diseased conditions it is supposed to cover. The term "chronic sick" is a sign of medical failure, of a failure to recognize a condition as treatable and, more important, as remediable.

I want first to mention those large wards full of immobile patients that are still so common in "chronic sick" hospitals. Here physical medicine has a great chance to show what it can do, because this is the problem with which most geriatric units are confronted when they start. It is necessary to get some of these patients treated with as economical use of physical medicine as possible—this is because economy in staff is likely to be more effective than lavishness, and because this will secure a more agreeable response from those who are interested solely in costs.

The physician will need to examine and classify all those diverse number of patients who have come under his care, and will choose a few who seem capable of some rehabilitation. A good physiotherapist or remedial gymnast is then essential, and a small daily PT class should be started, if possible in the ward. The exercises will need to be simple, and aimed at exercising the muscles of the arms, shoulders and back to begin with: catching a large, soft ball, raising the arms above the head, deep breathing, bending forward and backward and the like. The class should last for half an hour, and it will help if the wireless plays. Patients who at the start seemed unwilling to move will begin to do so, and, because the class takes place in the ward, other patients will in time ask to join in, while others will be seen doing the exercises from their beds, and then these can be asked if they would not like to join in the class, too. In this way, more and more patients will be found to express a wish to be rehabilitated. Emulation and competition are found to be just as valuable spurs to progress in the over 60's as in the teens.

But as more and more of the "chronic sick" wards and patients in the country get taken in hand, it is to be hoped that this early, hard, difficult work will become less and less common.

The next stage will see a combination of "chronic" and "acute" patients undergoing treatment. First, the classes in the wards should never stop. All old patients who are not in bed because of serious medical reasons should take part in them—they are good both for morale and physique.

For the next stage a rather different approach is required. Here again, one wants to be economical with staff.

The great problem with the aged who have been in bed for a long time is to get them to walk again. Once old people can be up for the most of the day in their own clothes, can feed themselves and can walk as far as the WC, they can lead some sort of normal life. Therefore, to walk is all important.

In all work for the aged, active movements, carried out by the patients themselves, are of far more use than passive movements. If patients have to be kept in bed for any reason they should, as soon as they are well enough, begin to exercise their quadriceps muscles, and their backs by means of a rope and broom handle attached to the end of the bed. Again breathing exercises in bed will help to keep an active circulation going and will use what amount of lung tissue is left to its full. No, or a minimum of, trained staff is required for this.

When the time comes for the patient to start to walk again one wants to see abolished for ever the picture of an old person being almost dragged along by two physiotherapists with her bottom stuck out in a triangular form. The patient should first learn to stand at the end of the bed in the manner first suggested by Dr. Marjory Warren, then, still holding on to the bed rail, should learn to stand on each leg in turn, then to walk a few steps sideways—then, but only then, when the patient has regained a good deal of confidence, should he be encouraged to walk forwards. Again, no walking machine—these are rather frightening, for there is nothing between full support and full freedom.

A wall bar and rubber matting with footsteps marked on it is useful in a ward: if in the gym, there can be a double bar, with a mirror at the end. Thus, the patient can walk with both hands on the bars, one hand, or no hand—the mirror enables patients to see their feet without peering down, and thus confidence is gradually established. There is no reason why patients should not practise as long as they can in the wards with the single hand bar—or in the corridors. But all this work is done with very little assistance from the physiotherapist, and, in this way, much waste of time and staff is saved. One physiotherapist can overlook the work of several patients, and see that nothing dire happens to them

A set of stairs, 3 or 4 steps up and down, is useful in a gym—it must not be forgotten that most old people find it more frightening to go down rather than up stairs.

Wall bars are useful for shoulder exercises, and a Balkan frame with springs can help in the strengthening of back muscles. Four- or three-legged sticks are useful for patients when they start to walk by themselves again, the three-legged one is really the best, for, when the outer leg is a bit longer than the two inner, the patient can bear down direct on the inner leg and save the extra strain of having to extend the arm to get all four legs on the ground.

Thus the staff of trained physiotherapists can be small, and a lot of the work be done by orderlies working under the supervision of a trained physiotherapist.

The preventive side seems to lie mainly in encouraging elderly patients to do exercises—preferably in their own homes, but if not, in classes in a gym to which they can be brought. Domiciliary treatment is popular, but it is extravagant in physiotherapists' time, and patients tend sometimes to be left on treatment when there is no real benefit to be obtained from it, because they never get seen either by their own doctor, a physician at the hospital or the physical medicine doctor: it may, however, have a limited value if properly and rigidly controlled.

Prompt treatment of disease in the elderly coupled with the knowledge that prolonged rest in bed is not only unnecessary but bad will do a great deal to make the task of the physician and of the physical medicine department easier. For example, the modern practice of getting patients on their feet within a few days of pinning a fractured femur shortens the period of treatment by many weeks—the patient never has a chance to forget how to walk.

Regular exercises, by restoring many elderly patients to a more or less normal degree of mobility, will reduce the proportion of incontinent patients in a ward, or even at home, and will thus ease the strain on both relatives and on nursing staff.

There should also be close working between the orthopædic department and the instrument maker—much good can come out of the treatment of a patient with, say, hemiplegia, by a combination of supervised and controlled exercises and springs and leg irons carefully designed to overcome foot drop and irremediable weakness of leg muscles.

Mr. L. Cosin: The role of physical medicine in the treatment of the disabilities of the elderly must be carefully defined if maximum benefits are to be obtained, for physical treatment in the field of geriatric medicine can be the basis of restoration of independence. It may well be that the degree of independence is not complete; this should not result in a misconceived passive acceptance of the inevitable, but rather in a spur to the physiatrist and his colleagues to attempt the maximal restoration of physical efficiency.

The gloomy prognosis of physicians when faced with this problem has resulted in many elderly patients being labeled "incurable" and "irremediable"; they were then incarcerated in "hospitals for the chronic sick" or "homes for the incurable" for many months.

Because of their classification and the implied prognosis, little treatment was provided, and least of all physical medicine. The sparsely staffed, overcrowded wards full of patients awaiting the inevitable were less a reproach to the hospital authorities then in charge than to current medical opinion. For two fundamental errors were made.

The first was the facile acceptance of the inevitability and irreversibility of pathological processes in the elderly. It was no fault of the medical profession, however, that in the absence of mercurial diuretics, the sulphonamides, and the later antibiotics, certain serious illnesses in old people were more common, and recovery rare. The routine use of these therapeutic agents has necessitated a complete reassessment of the care of the elderly within the last few years. Mortality due to certain diseases has been reduced so that the problem of morbidity in the elderly and some means of its reduction have become of great importance. For unless physical medicine solves the problem of geriatric rehabilitation a grave crisis must arise in providing sufficient hospital beds, not only for this age group but for others also. For an elderly person, whose period of morbidity may greatly exceed the average (about eighteen days) in a hospital bed, will be responsible for keeping out several other patients. This is occurring in Great Britain and other countries to-day. We see, then, that apart from the advantages of geriatric rehabilitation to the patient the pressure on hospital beds may be thus diminished.

The second, more serious error, was the failure to recognize the possibility of a restoration of physical activity in elderly patients with crippling conditions. The problem of long-term illness was then handed over to the nursing profession to handle.

In recent years the shortage of nurses has been greater than the shortage of hospital beds in Great Britain, so that a reservoir of "unstaffed" hospital beds has been available. With increasing numbers of nurses, however, the real shortage of hospital beds is beginning to appear.

The rapidly increasing numbers of the elderly in the next two or three decades, with their decreasing mortality rate and increased morbidity rate, will make more serious an already serious problem of hospital accommodation. It is within the sphere of physical medicine to ameliorate this problem, if not to solve it.

We must differentiate between the individual prescription of physical treatment for a condition occurring in an elderly person, as it might at any other age, and a planned course of geriatric rehabilitation. In the latter case especial attention must be paid to the several factors hindering physical recovery; chief of these may be the occurrence of more than one pathological process. Each process may be responsible for some degree of physical disability. We have usually accepted the teaching that the simultaneous occurrence of more than one major pathological process is a rarity, and this is undoubtedly true in the younger age groups. On turning to the higher age groups we can make no greater error. Most elderly patients are suffering from multiple pathological processes, some of them discrete. The wider dissemination of this fact, and its utilization, is clinically of great importance. For if the patient sustains another, or exacerbates an existing disease, however quiet previously, a series of nutritional, biochemical, and metabolic disturbances may be precipitated. Each one of these could be ample cause for keeping him in bed and physically incapable of painless, free and active movement. Without this, independence is not possible.

Added to the pathological and metabolic disturbances of the elderly we must consider also the emotional upsets associated with increasing dependence upon others. This may set in train faulty psychological reactions to illness, as a result of which there may be an acquired psychoneurotic anxiety state and various psychosomatic symptoms.

It is very important for the general physician to assess the impact of the multiple pathology upon the ageing organism, for thereby he is in a position to direct more effective treatment. But it is equally important for the physiatrist to assess these also. For upon the latter will fall the responsibility of providing a planned programme of rehabilitation. To carry this through successfully will require much patient investigation and individual assessment, which may vary in each case. These old people are frail, feeble folk, often with a conviction that life has been too burdensome even before they sustained the latest buffet of fate.

It falls to the physiatrist, then, to assess many factors which do not fall immediately within his sphere. If, however, his accepted aim is to restore the maximal degree of painless voluntary movement he must be prepared to accept the hypothesis that several other factors in other fields of medicine may be responsible for limiting his aims. How can he be in a position to achieve his acknowledged aims in his own field, then, unless it is accepted that his awareness of these other factors is a part of his work?

The answer is that the physiatrist must take a far wider view of the general problems of medical rehabilitation than the narrow technical interests of electrotherapy.

He must be prepared to investigate and assess the possibility of disabilities following surgical, medical, traumatic, psychological, sociological, and metabolic factors occurring in an old person. He will then be in a position to provide adequate schemes of rehabilitation where applicable. The aim of geriatric rehabilitation consists in the restoration to each elderly patient of the maximum degree of painless movement. This is usually attained as a result of treating the most important pathological process or ameliorating its effects.

The most systematic way of carrying out this programme is to aim at reducing the residual physical disability of each patient to as low a level as possible. A group approach to the problem must be made. Thus, nurses, occupational therapists, social workers, psychiatric social workers, and the many voluntary associations interested in social work and after-care, will find their place in this work.

The body has great physiological reserves which are not usually needed or made apparent. These reserves though not abundant in the elderly are, however, available for exploitation and development after pathological processes have reduced the functioning efficiency of one or more organs or systems.

Rehabilitation by physical methods, then, is scientifically sound in that it improves the ability of the body to deal with situations produced by exercise. This observation is applicable to patients of all age groups; once the pathological processes are no longer actively progressive and have become compensated by physiological adaptation, physical rehabilitation can be given with the expectation of improvement.

The point of importance is that unless far more careful physical assessment of capacity for exercise in the elderly is carried out we shall not be exploiting the body's ability to improve by using physical methods of retraining.

It is important, however, to differentiate between purely physical causes of disability and the so commonly associated psychological and sociological factors in the elderly, which hamper physical rehabilitation. It is, therefore, absolutely essential for the physiatrist to make these assessments before arranging long courses of physical treatment.

Whatever the presenting symptom complex it is helpful to consider each patient to be suffering from a series of slowly progressive pathological processes, one more advanced than the others. Each of these may have resulted in diminished function due to decreased available physiological reserves. The resultant poor physical condition will be expressed generally as frailty, and locally as disability.

It is the function of the physiatrist in the geriatric unit to use all therapeutic weapons by which the physical function of the body as a whole, and certain systems in particular, can be maintained, and then increased.

This will be done by exploiting the difference between the lowered physical function due to active disease and that due to failure to utilize available physiological reserves. Both must be accurately assessed, and medical treatment arranged for the former factor, before rehabilitation can be arranged for both.

It is now possible to hazard an explanation of the common gloomy prognosis of the elderly. Their diminished physical function has been more often thought to be due to the effects of one pathological process alone, rather than the summation of such processes, and the failure to utilize available physiological reserves.

One most important problem of the elderly, whether in or out of hospital, lies in their feeling of basic insecurity due to loneliness.

The basic sociological problem of providing continued care must be faced and solved before the maximum of physical recovery can be expected. Therefore, the social worker, almoner, or psychiatric social worker should ascertain any factors hindering recovery; thus can the appropriate steps be taken as early as possible in the natural history of disease; thus can the recovery of the patient be hastened without the excessive and wasteful use of the physiotherapist's time.

It is essential to realize that organic disease in the elderly, expressed in terms of a complaint of pain, can be the passport to increased security. There have been many occasions when I have ascertained that an old person's complaint of pain and disability, while under treatment in hospital, has improved up to the point where increased activity and re-education in walking should commence. At this stage, however, an exacerbation of the local condition or generalized complaints concerning staff, facilities, or the treatment result in a slowing or discontinuing of physiotherapy. It is the duty of the physiatrist at this stage to reassess the whole situation so that sociological factors hindering recovery can be ascertained and dealt with appropriately. There is no point in blaming the unfortunate patient for refusing to acquiesce to a line of conduct which in his opinion is not a course of treatment and which would only result in less personal comfort and ultimately more personal pain.

The complaints of relatives also must be considered from this viewpoint, and while justified complaints need correction, an examination of the whole psychological situation may reveal other facts hindering the patient's recovery.

Dr. A. Talbot Rogers: From the point of view of a general practitioner interested in what physical medicine can do for older patients, it is a comfort to know that when an old patient has to be sent into hospital he can receive there the greatest possible measure of rehabilitation, but I agree with Lord Amulree that physical medicine also has a preventive function and that it is this side of the specialty that now most needs development. A general practitioner does not wish to unload his elderly patients on the hospitals; most of the old people want to remain independent as long as they can, and physical medicine has an important part to play in helping them to do so. But this cannot be done by the special in-patient departments alone. All physical medicine departments should take their share of this preventive work for the aged, as out-patients as well as in-patients.

The general practitioner sees many different types of elderly patient who are in danger of losing their independence through some form of crippling disability. The common types of cases in which the physical medicine team could do so much to delay the final loss of independence are: osteo-arthritis, post-traumatic arthritis, the old rheumatoid arthritic or post-traumatic case with secondary osteo-arthritis, new cases of rheumatoid arthritis (for these occur more commonly in old people than is often recognized), hemiplegia, chronic bronchitis and bronchiectasis, and painful crippled feet. Much could be done by class work in hospital to teach these old people how to retain residual movement and muscle tone. Simple methods of heat treatment, particularly the use of paraffin wax baths, could also be taught to them for their use in their own homes. A certain proportion would not be able to go to the hospital, e.g. the hemiplegic. If these patients could be reached by a mobile physiotherapy unit so that the earliest possible help could be given in their rehabilitation, they could be brought to hospital to continue their treatment as soon as they were sufficiently mobile. The opportunity this would give them to meet other people suffering in a similar way as themselves, and by emulation and competition to try to regain strength and become independent again, is of very great value.

The occupational therapy department can also help in the re-ablement of these old people. It is of great recreational and social value to the elderly, but in addition it could provide instruction to the disabled in special "tricks" and the use of gadgets which would enable them to dress, shave and feed themselves. Very many types of useful gadgets have now been designed for the use of the disabled in their daily domestic tasks. The occupational therapy department is the best information centre for the design, supply and demonstration of these implements.

In some physical medicine departments there has been a tendency to concentrate on the treatment of the acutely ill patient. I believe that every hospital should provide help for the old people of the community served by that hospital. These people are very grateful indeed for everything that can be done to help them remain self-sufficient and those departments who help old people in this way have found their work most rewarding.

Section of Orthopædics

President—H. JACKSON BURROWS, M.A., M.D., F.R.C.S., F.R.A.C.S.

[*December* 2, 1952]

Hip Arthroplasties and Their Exact Technique [*Abstract*]

By J. J. HERBERT, M.D. (*Aix-les-Bains*)

DR. HERBERT had studied the tissue-reactions about vitallium cups and acrylic prostheses used in arthroplasty (1952). He stressed their function of transmitting power and weight as well as allowing movement. A secondary operation after cup arthroplasty revealed a lining of smooth fibrous tissue over healthy bone. Necropsy three years after insertion of an acrylic head revealed similar changes at the upper lip of the femoral stump; but the lower lip presented bone sclerosis and some cartilaginous metaplasia in its covering, the responses to pressure. No foreign body reaction was evident. A prosthesis should distribute weight widely and equally, and its insertion should be planned from tracings of full-face radiographs of the femoral neck. In drilling for a Judet prosthesis a special apparatus would compensate for the deviation of the axis of the neck from the centre of the head. Contrary to British opinion, Dr. Herbert favoured the vitallium cup in ankylosing spondylitis, and for this alone. Prostheses did not arrest degeneration: they only changed its site.

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Recurrent Instability of the Ankle—a Method of Surgical Treatment

By DAVID L. EVANS, F.R.C.S.

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FIFTEEN women and four men with recurrent instability of the ankle treated by transposition of the peroneus brevis tendon form the subject of this short paper. The average age of these 19 patients was 34.

Each gave a history of an original acute sprain. After this, at intervals varying from weeks to years, the ankle gave way and "went over" inwards. The cause was usually trivial, and often unknown. The ankle was temporarily painful and swollen. Resolution, however, occurred quickly. The only constant clinical finding was increased passive inversion. X-ray in forced inversion—without anæsthesia, because there was little or no pain—usually revealed tilting of the talus within the ankle mortice. This is quite a different picture from the acute sprain, a dramatic occurrence, with marked signs and prolonged pain and incapacity.

Clinically and radiologically there were two distinct groups. The first comprised 14 patients—10 women and 4 men. These showed increased passive inversion of the affected foot and corresponding unilateral tilting of the talus. The second comprised 5 patients—all women. These showed increased passive inversion of both feet, and bilateral tilting of the talus, either to the same or a varying degree.

At operation, in most patients the capsule of the ankle-joint and the calcaneofibular fasciculus of the lateral ligament were found ruptured. In some, the capsule and ligament were intact but sufficiently relaxed to permit tilting of the talus.

Many operations of varying complexity have been used in treating this condition. These include tenodesis (Nilsonne, 1931), ligament reconstruction (Elmslie, 1934), and combined tenodesis and ligament reconstruction (Watson-Jones, 1940). The use of the peroneus brevis tendon is common to most of these operations. A simple operation—transposition of the peroneus brevis tendon—is now described.

Through a 4-in. (10 cm.) straight or J-shaped incision behind the fibula, the peroneal tendons are identified. The tendon of the peroneus brevis is divided at the upper limit of the incision. The distal end is stripped of its lowermost muscle fibres, and dissected free to the back of the lateral malleolus.

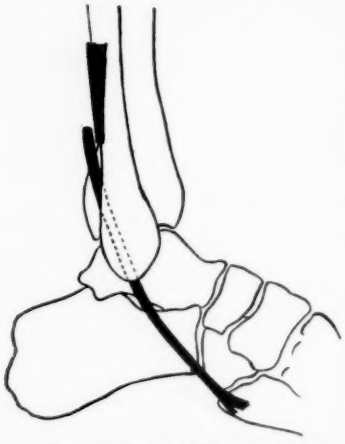

FIG. 1.—Showing the course of the transposed peroneus brevis tendon.

Here it is withdrawn through the superior peroneal retinaculum to below and in front of the lateral malleolus. A 3/16 in. (0·5 cm.) drill hole is made diagonally forwards and downwards through the lower end of the fibula. The tendon is threaded back through this drill hole, and with the foot held in slight eversion, is reattached to the proximal end with any necessary overlap (Fig. 1). Threading is facilitated if the lower opening is enlarged with a small gouge or burr. The wound is closed, and a below-knee plaster applied with the foot at right-angles and in the mid-position. This plaster is changed after three weeks and a walking plaster substituted. This is removed after a further three weeks, when normal walking is started.

Of the 19 patients, 14 were reviewed after three and a half years to eight months.

All patients had limitation of inversion of the foot, and there was usually no other abnormality. Swelling did not occur after the first six months. In some, the transposed tendon could be seen and felt acting above and below the fibular tunnel. In others a tenodesis had resulted. The time off normal activities averaged two months, though some patients resumed sedentary occupations earlier in plaster.

Twelve results were good, with no recurrence of instability or other symptoms. One was fair, after a post-operative deep vein thrombosis—the only complication encountered ; except for some residual swelling of the leg, the functional result was satisfactory. One was poor; the patient had some pain and swelling and marked restriction of inversion of the foot, but nevertheless she regarded the operation as worth while.

Of the many operations described, simple transpcsition of the peroneus brevis tendon would appear, on a short follow-up, to warrant further trial.

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The Use of Radioactive Phosphorus in Early Detection of Avascular Necrosis in the Femoral Head in Fractured Neck of Femur

By G. P. ARDEN, M.B., F.R.C.S., *King Edward VII Hospital, Windsor* and N. VEALL, B.Sc., A.Inst.P. *M.R.C. Radiotherapeutic Research Unit, Hammersmith Hospital*

THIS is a preliminary report with a follow-up which is too short for any final assessment. It is, however, already obvious that a larger investigation should be carried out.

Avascular necrosis in the femoral head occurs in about 30% to 40% of cases of fractured neck of the femur treated by nailing, and is commonly ascribed to vascular damage at the time of injury.

The introduction of radioactive isotopes has given us a new method of investigating the blood supply of human tissues. Radioactive phosphorus (P^{32}) is the most suitable isotope for this work. It emits β rays. These are easily detected but their range is limited, 0·1 mm. of tissue absorbing 90%. The half-life of P^{32} is 14·3 days, and the bulk of the isotope is excreted from the body in the urine and faeces fairly rapidly, the blood ceasing to be radioactive a few days after injection of P^{32}; the skeleton, however, continues to be appreciably radioactive for a few weeks.

Technique.—This isotope is given in doses of 1 to 2 c.c. intravenously as a sterile isotonic buffered phosphate solution containing approximately 200 mc. of P^{32} one hour before the nailing operation. The usual nailing technique is carried out, and two samples of bone are removed, one from the trochanteric region as a normal control (Fig. 1) and the other from the head of the femur (Fig. 2). These samples (100–150 mg.) are removed with a Harris's bone biopsy drill under X-ray control. They are dried and weighed, and their radioactive content is measured on a Geiger counter. The result is expressed as $\frac{\text{counts/mg./min. in trochanter.}}{\text{counts/mg./min. in head}}$

FIG. 1.—Hollow drill removing sample from trochanteric region.

FIG. 2.—Hollow drill removing sample from head of femur.

FIG. 3.—Needle counter in head of femur.

Results.—Tucker in Liverpool was the first to use this method in this country. He described the results first obtained in animal experiments and then in 12 patients with a fractured neck of femur with an eighteen-months' follow-up. His results confirmed the value of this method (Tucker, 1950).

I have repeated this investigation using a similar technique in 45 cases. 22 have been followed up for seven to twelve months. These are analysed in detail. 6 were cases of intertrochanteric fracture as a small control series in which the blood supply of both samples should be normal.

	RATIOS IN CONTROL SERIES	
Intertrochanteric series (control) 6 cases	1·7/1	2·5/1
	1·5/1	1/2
All fractures united, except in one patient who died	1·5/1	1·7/1

The results in a series of fractured neck of the femur were as follows:

	Ratios	Results
9 femoral neck fractures with normal ratios	1·6/1 1/1 1·7/1 1·7/1	All fractures united and normal progress for seven to twelve months after operation
All nailed	1/1	Nail slipped out: Re-nailed and fracture united
	1·2/1	Nail slipped out: Judet performed
	0·6/1	Nail cut out: Judet performed
	1·2/1 2·5/1	Nails cut out Judet refused by patients Non-union occurred

	Ratios	Results
2 femoral neck fractures with borderline ratios	3·3/1	Nail cut out Judet performed
	2·8/1	Normal progress for nine months. United
5 femoral neck fractures with abnormal ratios	20/1 12/1 10/1	Initial Judet arthroplasties
	30/1	Nailed. Unfit for Judet. Died one month later
	7/1	Nailed, having refused early Judet: still ununited after nine months. Now awaiting Judet

5 out of 16 definitely abnormal = 30%.

False readings may occur for the following reasons: (1) Contamination of specimens by radioactive blood; (2) Too long an interval between giving P^{32} and removing samples; (3) Variation in samples from different parts of the head; (4) Delay between removing samples, as the P^{32} content of the bone steadily rises.

Recent modification.—More recently it has been possible to take direct readings at the time of operation by inserting a needle counter up into the head of the femur and connecting this with a clinical monitor which automatically counts the β rays picked up by the point of the needle, the position of which is checked by X-ray (Fig. 3). The drill hole should be syringed out with saline between readings to remove any radioactive blood which might lead to a false reading. It is thus possible to decide whether the blood supply to the femoral head is damaged or not, by a procedure which can be completed in twenty to twenty-five minutes.

This direct method has three advantages: (1) A decision can be made within twenty to twenty-five minutes whether to nail the fracture or replace the femoral head by a prosthesis; (2) Several readings can be taken to exclude errors; (3) The rate of P^{32} absorption by the bone can be measured over a five to ten minute interval, this being probably the most accurate indication of the blood flow.

Conclusions.—This small series, together with Tucker's, suggests that it may be possible to detect early avascular necrosis by this method.

Should further investigation prove this method to be of value it may be possible to nail only those fractures that will unite and to carry out a prosthetic replacement of the femoral head in the other cases, thus obviating the later complications of avascular necrosis.

Part of the cost of this investigation was defrayed by the Mocatti Research Fund.

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Correlation Between Changes in the Spinal Cord and Muscle Paralysis in Poliomyelitis—A Preliminary Report

By W. J. W. SHARRARD, F.R.C.S.

Method of Study

Although the grey matter of the normal human spinal cord has been studied extensively during the past sixty years, the published results are inadequate to form a basis for qualitative and quantitative comparison with spinal cords affected by poliomyelitis. Serial transverse sections of 15 μ thickness, cut in paraffin wax and stained with eosin azure to show their nerve cells, were therefore made of the whole of the lumbosacral cord and of various levels in the thoracic cord. With a projection microscope, an image of each of these sections was projected at a magnification of 100 times and an accurate drawing was made of all nerve cells in the grey matter: thirty images were superimposed to produce a "cell chart" (*see* Fig. 1). This process was repeated for each sequence of thirty sections to provide a series of cell charts for each lumbosacral cord studied. An exactly similar technique was used for normal and pathological cords.

Normal Cord—Anterior Horn

The nerve cells in the anterior horn can be differentiated by size into three main types:

(*a*) *Large cells* of size 60 to 100 μ; these are collected into more or less discrete groups which are only faintly indicated in single sections but are easily distinguished in cell charts. Most of the axons arising from these cells pass into the ventral roots to supply voluntary muscle.

(*b*) *Medium-sized cells* of size 30 to 60 μ are seen in greatest numbers in the intermediolateral region of the thoracic cord and in the sacral cord. They are probably cells whose axons supply the motor component of the sympathetic or parasympathetic nervous systems.

(*c*) *Small cells* of size less than 30 μ are diffusely scattered in the more posterior and medial part of the horn and in the regions not occupied by larger motor cells. Their function is not certainly known, but some of them may have an internuncial function.

The anterior horn at any given level shows an outline characteristic of that level and a typical arrangement of its large motor cell groups. If these groups, as seen in transverse section, are studied in conjunction with longitudinal sections, they can be seen to represent columns of motor cells. The existence of these *motor cell columns* has long been recognized, but their more precise topography and functional significance has only been identified in recent years. The results of analyses of chromatolytic changes in the large motor cells after amputation or nerve injury, both in man and in the experimental animal, suggest that the columns represent peripheral musculature in muscle groups; that is to say there is one column for the intrinsic muscles of the feet, another for the hamstring muscles, and so on.

The muscle representation of many of these columns is well established: a few are doubtful. Quite sufficient is known to make a satisfactory analysis of the function of the remaining large motor cells in the cord after an attack of acute anterior poliomyelitis.

Pathological Material

For a spinal cord to be suitable for analysis, two criteria must be fulfilled: (1) The patient must have died not less than four months after the onset of the disease, in order to allow time for resolution of acute inflammation and to ensure that any remaining nerve cells, and particularly large motor cells, are functioning cells; (2) A detailed muscle chart of the paralysis must have been obtained.

Such specimens are rare. The results so far obtained are based mainly on a complete analysis of the lumbosacral cord of a woman aged 23 who died twenty-two months after the onset of her disease.

Cell Destruction

Cell destruction in the anterior horn was not diffusely distributed along the length of the cord, but occurred in more or less discrete "foci" which occupied the length of two, three or more spinal cord segments. Between these foci were regions almost normally populated (Fig. 1).

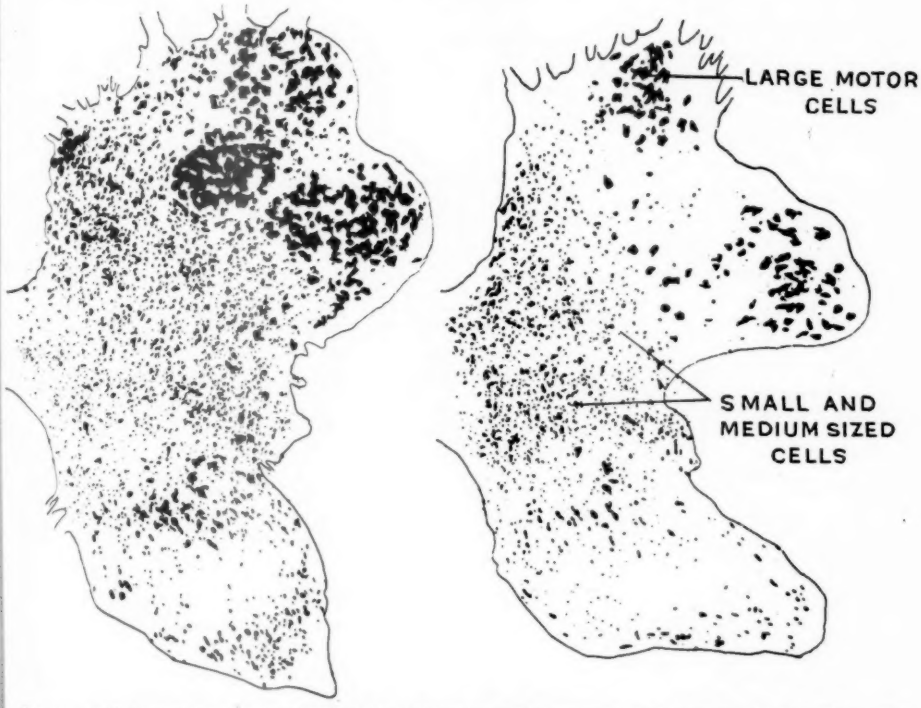

FIG. 1.—Cell chart at level of the middle of the fifth lumbar spinal segment. *Left*, normal. *Right*, poliomyelitis. Cell destruction is confined to the large motor cells, and is greatest in the central column. (The anterior horns lie towards the top of the page; the medial sides face to the left.)

In regions least affected, only large motor cells had been destroyed, the centrally and posterolaterally situated columns of these cells being involved more than those lying anteriorly and medially. Small and medium-sized cells were almost unaffected—a marked feature in the thoracic cord, where the medium-sized sympathetic cells lying in the intermediolateral horn remained intact in spite of considerable loss of large motor cells. Although one of the lower limbs in the patient concerned showed moderately severe vascular changes of the type seen in poliomyelitis, and the opposite lower limb was much less affected, the sympathetic cells were largely spared on both sides of the cord and to the same degree (Fig. 2).

In regions of moderately severe destruction, where all large motor cells had disappeared or where only two or three cells remained in a cell chart, only a slight diminution in the number of small and medium-sized cells could be seen, mainly in the regions close to the lost motor columns.

In regions of severe destruction, for instance at the centre of a large "focus", the loss of nerve cells of all sizes was in some charts almost complete and even extended into the base of the posterior horn (Fig. 3).

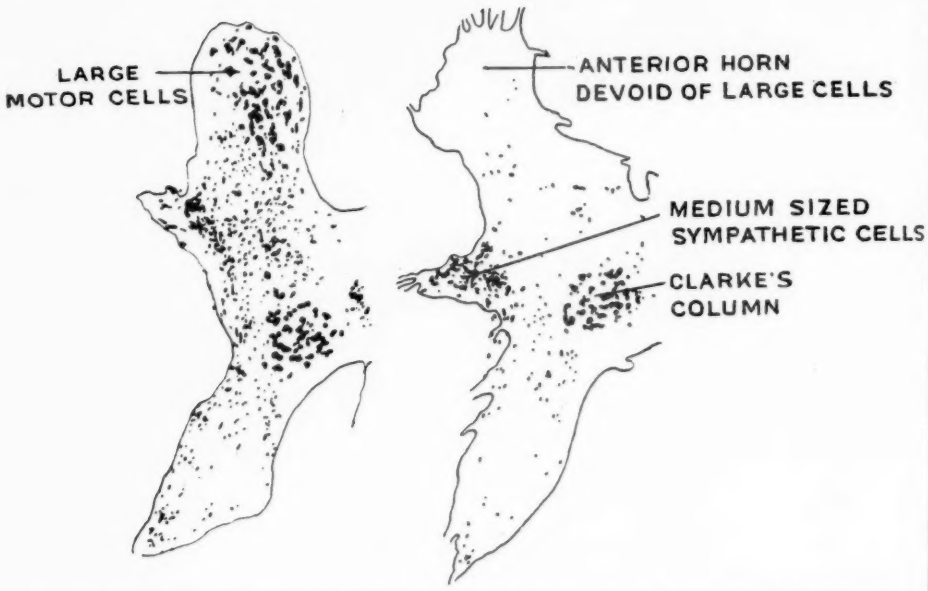

FIG. 2.—Cell chart at the level of the eighth thoracic spinal segment. *Left*, normal. *Right*, poliomyelitis. All the large motor cells have been destroyed; medium-sized and small cells close to the lost motor cells are diminished in number but the medium-sized sympathetic cells in the intermediolateral horn are completely intact, as are the large cells of Clarke's column. (The medial sides face to the right.)

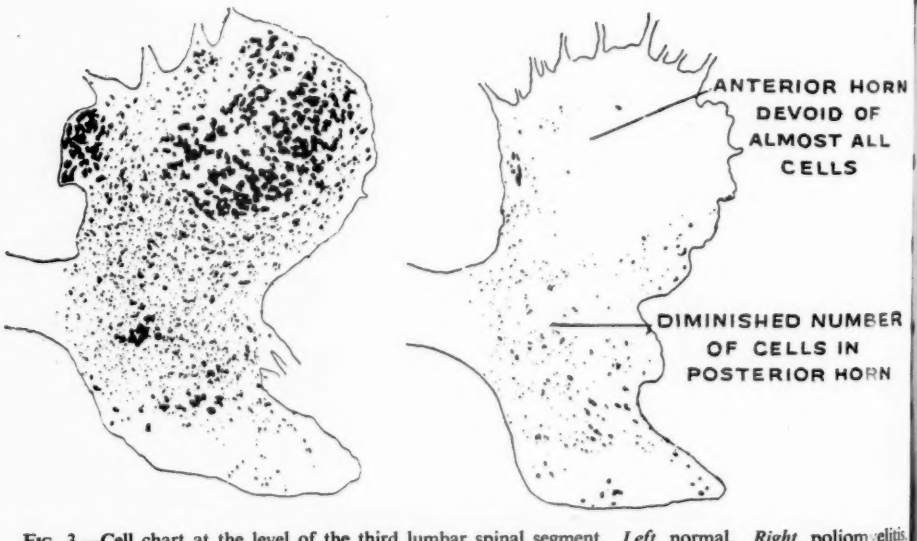

FIG. 3.—Cell chart at the level of the third lumbar spinal segment. *Left*, normal. *Right*, poliomyelitis. Complete loss of large motor cells (except for one cell in the anteromedial column) and considerable diminution in the number of medium-sized and small cells, extending into the base of the posterior horn. The lower end of Clarke's column has been affected. (The medial sides face to the left.)

Correlation with Muscle Paralysis

Correlation with muscle paralysis was surprisingly good. Whenever a muscle group had been clinically paralysed, no nerve cells could be found in the cord relative to that muscle group. Conversely, the presence of any large motor cells in a given region of the cord corresponded to clinical evidence of activity in the appropriate muscles. The number of motor neurones necessary to produce clinically detectable muscle activity was much fewer than had been expected. For instance, the adductor muscles, which had been graded power 2 (Medical Research Council grading), could be shown to be supplied by a total of *not more than* 50 large cells; that is, the total number of these cells present in the second, third and fourth lumbar segment. The hip rotators were also clinically acting and some of this total of cells (together with cells remaining in the ventral part of the anterior horn segment below the fourth lumbar) almost certainly supplied the obturator and gemelli muscles. Correspondingly, a clinical grading of 5 was present in two muscle groups whose motor neurones had been reduced by at least 50%. Whenever a muscle or muscle group on one side of the body had been clinically graded at a power higher than its fellow in the opposite limb, there were correspondingly more large motor cells in the appropriate columns on that side of the spinal cord than on the opposite side.

Further work is in progress on this and similar material, the results of which will, it is hoped, be published later in greater detail. It is possible that this study and further research of this kind may clarify the part played by nerve cell destruction in determining not only the degree of muscular paralysis but also the characteristic distribution of it in poliomyelitis and the varying capacity for recovery seen in different muscles. This work has been undertaken at the Institute of Orthopædics, Royal National Orthopædic Hospital, under a grant from the Medical Research Council.

Neo-natal Volkmann's Syndrome

By G. M. Bedbrook, M.S., F.R.A.C.S., F.R.C.S.

Seventy-seven years after Volkmann originally described his syndrome in muscle, his conception of its ætiology is held to be correct.

Case history.—A surviving twin was delivered by Cæsarean section on 7.7.52. At birth it was noticed that the whole right upper limb of the otherwise normal baby was œdematous, flaccid and pale. The wrist and fingers were contracted. The œdema had a sharp line of demarcation in the supra-clavicular areas. There was no record of traction or cord pressure.

By the fourteenth day the swelling had gone. Power had returned to the upper arm, but it was wasted and the biceps and triceps jerks were absent (present in the other arm). The muscles distal to the elbow still showed complete flaccid paralysis and wasting, with loss of supinator jerk. The forearm muscles were indurated, and there was marked flexion contracture of the wrist and fingers like that seen in Volkmann's ischæmic contracture. The radial pulse was present.

By the end of four months of splinting and stretching, recovery was virtually complete.

There were two conditions, an ischæmic contracture and a concomitant brachial plexus lesion. It seemed clear that the only possible cause was very brief circumferential pressure on the shoulder girdle. The brachial plexus lesion proved to be a mixed one, partly a neurapraxia and partly an axonotmesis.

It is likely that the contracture was coincidental with the brachial plexus lesion rather than its sequel, because (*a*) the œdema was well-marked, (*b*) the contracture was much more severe than that seen in ordinary neo-natal palsies, and (*c*) the two conditions began together.

The youngest previously recorded patient with Volkmann's contracture was aged 16 months (Cahuzac and Jung, 1946). 107 cases from the literature included one in a boy aged 2 years (Thomas, 1909).

The association of Volkmann's contracture and nerve lesion is well known (Thomas, 1909; Holmes, Highet and Seddon, 1944–45; Steindler, 1917, 1936). Both may be due to ischæmia, and this seems probable in the present instance, but the initial extent of paralysis makes an independent plexus lesion possible.

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Types of Injury in Run-Over Lower Limbs

By R. S. HENDERSON, F.R.C.S., and L. M. ROUILLARD, F.R.C.S.Ed.

WHEN a vehicle wheel passes over a limb, two distinct types of injury have been noted. In the first, closed fractures may be associated with little damage to soft tissue. In the second, soft tissue damage is of primary importance: skin flaps are often avulsed and crushed, but the extent of damage may not be immediately apparent; fractures are usually comminuted. From our experience it has seemed possible that in the first variety the limb is crushed by a single blow from a revolving wheel, whereas in the second a shearing force grinds the limb between the road surface and a skidding wheel, locked by suddenly applied brakes.

In the first type, treatment is relatively simple. The second group presents the difficulty of replacing lost skin in the presence of comminuted and unstable fractures. In these, it is rarely possible at first to predict how much soft tissue will survive, because at the time of injury damaged skin may appear to be viable; necrosis, probably due to thrombosis of small vessels, is delayed for varying periods. Such a sequence of events is seen when a hand is ground in a press or crushed between rollers. If the danger of delayed necrosis is overlooked, the surgeon may be tempted to replace loss by immediate full thickness cover such as a cross-leg flap (Gissane, 1950). If this is combined with internal fixation and the surrounding skin later dies, disaster may be expected.

In cases showing this gradual soft tissue necrosis, we have deferred skin replacement until sloughs have become well defined. They have then been excised, with any dead or infected bone, and the area has been covered with split skin grafts. Only when skin healing is complete is consideration given to replacing the grafted area by a flap or pedicle. If, as in 2 of the cases described below, a constricting collar of scar forms at the site of grafting, then a flap or pedicle, applied to bridge the collar, may prevent or diminish œdema beyond it (Mowlem, 1948).

ILLUSTRATIVE CASES

Case I.—Man, aged 39. Knocked down by a motor car which ran over both legs. The circumstances suggested that the driver had no time to apply his brakes. Examination showed closed, oblique fractures of both tibiæ; the skin of both legs was quite undamaged. Plasters were applied after reduction, but severe illness from fat embolism prevented their being changed, so that displacement of the fractures recurred. After four weeks both were unstable and open reduction with internal fixation was carried out. The skin over the fractures remained healthy throughout, and both fractures united in about three months.

This is an example of the first type of injury, probably caused by a single blow to both legs from a revolving wheel, before the application of brakes.

Case II.—Woman, aged 56. Fell from a moving bus, a wheel of which passed over her left femur. The driver applied his brakes immediately she fell. There was an open fracture of her left femur with gross deformity; a ragged wound extended from the gluteal fold to the knee-joint, exposing the distal end of the proximal fragment, over which were stretched the popliteal vessels and the divisions of the sciatic nerve. The wound was excised and the fracture reduced with difficulty. The soft tissue was sutured back loosely and the limb slung lightly in a Thomas's splint.

FIG. 1. *Case II*).—Showing healed collar of scar tissue.

FIG. 2 (*Case II*).—Showing skin graft bridging the collar of scar tissue.

The skin flap gradually became necrotic and, by the tenth day, a broad collar of slough completely encircled the thigh. It was excised and replaced by split skin grafts; these survived and the area healed in three weeks. Union of the fracture took place in a hip spica in about three months. Subsequently, œdema after exercise appeared beyond the collar of scar tissue that now encircled the thigh (Fig. 1). A tube pedicle was therefore brought down from the abdomen via the wrist (Mowlem, 1948), bridging the collar on the medial side of the thigh (Fig. 2). Within six months of injury, the patient was able to walk considerable distances without swelling of the limb.

This injury was of the type that could be ascribed to a shearing force between road and a wheel locked by brakes.

Case III.—Man, aged 61. Knocked off his bicycle by a lorry which passed over both legs. There was a supracondylar fracture of the left femur with no skin damage. The right tibia and fibula had suffered an open fracture with comminution, and a ragged wound extended obliquely half-way round the leg. The skin looked viable. The wound was excised and sutured. Three weeks later, it was found that a width of 5 cm. of skin on each side of the suture line had become gangrenous. This was excised and replaced by split skin grafts. Healing took place in about three weeks but union of the fractured tibia was delayed and a painful œdema below the grafted area appeared. The scar was replaced by a cross-leg flap and, two months later, the tibia was exposed through the flap and the fragments were fixed by bone graft. Union occurred and the patient returned to work as a labourer. The left femur united in three months and the skin over it remained healthy.

It is conceivable that in this case a revolving wheel damaged the left femur, sparing the soft tissues but that, when brakes were applied a fraction of a second later, the right leg received the full shearing force of a skidding wheel.

Slack (1952) has described the effects of friction in road injuries. He has drawn attention to the type of fracture caused by a run-over injury which, covered by apparently intact skin, is enclosed in plaster after manipulation. He points out the danger, in this type of injury, that delayed necrosis may occur inside a plaster cast. Later this may give rise to litigation.

Our thanks are due to Mr. S. L. Higgs and Mr. Rainsford Mowlem for permission to publish reports of patients under their care.

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Tumours of the Proximal Limb Bones and Hip Simulating Intervertebral Disc Lesions

By J. C. McNEUR, F.R.C.S., F.R.A.C.S.

Institute of Orthopædics, Royal National Orthopædic Hospital, London and Stanmore

IN these days when an intervertebral disc lesion has become a popular diagnosis, and is considered first in the differential diagnosis of most cases of pain in the lumbar or cervical spine radiating down the leg or arm, it is easy to forget that other lesions—situated outside the vertebral column—may, and often do, give a similar history with radiating pain.

Six cases of bone tumour involving the femur, pelvis and upper humerus are here presented, in all of which radiating pain, sometimes of root distribution, was ascribed to an intervertebral disc lesion and treatment given accordingly for a time (*see* Table I).

TABLE I

Case	Age	Symptoms	First Diagnosis	Treatment	Final Diagnosis	Reason for Local X-ray
I	27	Lumbar pain radiating down the left leg	Lumbar disc lesion	Physiotherapy. Plaster jacket	Osteosarcoma neck left femur	Limited movements left hip (Fig. 1)
II	36	Pain radiating down the right shoulder and arm	Cervical disc lesion	Moulded leather cervical collar	Chondrosarcoma right humerus	Tenderness upper half of the humerus (Fig. 2)
III	34	Lumbar pain radiating down the left leg	Lumbar disc lesion	Physiotherapy	Chondrosarcoma left femur	Appearance of swelling in left thigh
IV	47	Increasing lumbar pain radiating down the right leg	Lumbar disc lesion	Physiotherapy	Fibrosarcoma right femur	Swelling of the right knee
V	61	Lumbar pain radiating down the right leg. Nephrectomy for hypernephroma one year before	Lumbar disc lesion	Physiotherapy. Manipulation	Secondary hypernephroma acetabulum	Pathological dislocation of the right hip
VI	38	Radiating pain down the right hip and leg	Lumbar disc lesion. ? Cauda equina tumour	Physiotherapy	Secondary carcinoma ischium from the lung	Negative findings in the spine

FIG. 1 (*Case I*).—Osteosarcoma of the inferior aspect of the neck of the left femur.

FIG. 2 (*Case II*).—Chondrosarcoma involving the upper half of the right humerus.

Radiological examination of the part of the spine suspect of a disc lesion is usually made as a matter of course, and vertebral lesions such as primary or secondary tumours seldom escape detection in good films. The usual radiographs of the spine, however, include little of the pelvis and none of the femur, shoulder, or humerus, and in consequence lesions mimicking a "disc" but situated outside the spine may easily be missed unless clinical signs lead to a more extensive radiological investigation. It is suggested that in all cases lacking objective neurological evidence of a root lesion—for instance changes in power, sensibility, or reflexes—and in the absence of accentuation of pain on coughing, radiographs of the proximal humerus or femur should be taken. Even so, the very best radiographs may fail to reveal quite extensive secondary growths, as was shown by Shackman and Harrison (1948), and will certainly fail to do so if they do not include the affected part—a fault in 5 of our cases. It is also obvious that clinical examination of all cases of "intervertebral disc lesions" should always include the proximal limb joints.

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Section of General Practice

President—E. P. Scott, M.B., M.R.C.S., L.R.C.P.

[*October* 15, 1952]

Diagnosis in General Practice [*Abstract*]

VALEDICTORY ADDRESS

By J. D. Simpson, V.R.D., M.D., M.R.C.P.

The sentimentalists, both inside and outside the profession, love to speak of the general practitioner of Medicine as Guide, Philosopher, and Friend, and to think of him only as a signpost to the specialized departments of a hospital, but in fact he has a far less nebulous function.

Firstly, he must be a diagnostician who can make a primary diagnosis with the aid of the history and his own clinical examination, without the use of ancillary aids.

Secondly, he must know how and where his diagnosis can be confirmed or disproved expeditiously and efficiently, and how to initiate specialized treatment when required.

Thirdly, he must be skilled in prolonged therapy, psychological, pharmacological and occupational, and be able to carry on work which specialized experts have started.

Fourthly, he must have a profound understanding of his patients' environment in its fullest sense, their work, their home surroundings, their families and their emotional lives.

Disease, as the general practitioner sees it, is the reaction of some pathological process, and/or physiological or psychological stress on the personality of the individual. Therefore, before a full diagnosis of disease can be made, all these factors must be appreciated and assessed. Obviously, if the pathological process is a neoplasm, the other two factors will be relatively unimportant, but if, on the other hand, the patient is suffering from a psychosomatic disorder, the stress and the personality are all-important. There is an infinite grading between these two extremes.

The patients fall into four groups, as shown:

Table I

Groups	Pathological process	Personality	Physiological psychological environment
1. The *old* patient with the *old* disease	Known	Known	Known
2. The *old* patient with the *new* disease	Unknown	Known	Partially known
3. The *new* patient with the *old* disease	Known (from notes or story)	Unknown	Unknown
4. The *new* patient with the *new* disease	Unknown	Unknown	Unknown

Each of these groups presents special interests, difficulties and pitfalls. In the first and second groups we may be lulled into a sense of false security in that we know all about the patient, and miss some disease which has been present all the time or has developed insidiously and has been masked by the familiar cough or backache. Here it is that the group practices which are developing all over the country are especially valuable, for a colleague may well notice a sign which has been missed by the regular medical attendant. In my own recent experience, I have missed the insidious development of hyperthyroidism in a woman who was suffering from chronic alcoholism; and uræmia due to an enlarged prostate in a man who had retention of urine with overflow, but no difficulty in passing urine on examination. He did, however, have a headache and a very dirty tongue. Failure to evaluate these symptoms led to the mis-diagnosis.

The third group of cases, includes the new patient with the old disease, the patient who has just come into one's practice and has been under the care of his or her doctor for years. The group might well be described as the old patient with the new doctor. Here it is necessary to proceed with great caution. Firstly, we must satisfy ourselves that there is no immediate medical urgency, and then await the notes from the previous doctor—otherwise we start a whole series of unnecessary investigations which could have been avoided by a little patience. Here it is that the value of the Health Service Medical Card is becoming apparent, for we can gain great insight into the personality of the patient from consideration of his previous illness, apart from having notes of special examinations and the opinion of his previous doctor as to the diagnosis. As a counsel of perfection, this opinion may well be written on a separate continuation sheet when the patient is transferred from one list to another.

In the fourth group, all the factors are unknown. The diagnosis must be made as quickly as possible. Knowledge of the prevalence of epidemic diseases in the district, of the occupational hazards of the patient and a readiness to appreciate clues of any sort can be used to make the primary diagnosis. A consultation for an extremely trivial condition is often the excuse to come to the doctor to discuss a far more serious psychiatric or psychoneurotic problem.

In modern medicine it is necessary to confirm the original clinical diagnosis. In general practice the therapeutic test is one very important method. The exhibition of a specific drug which cures the disease confirms the diagnosis, e.g. Vincent's angina is cured by penicillin; a very high proportion of cases of impetigo also are controlled by penicillin; but if the rash does not clear in a few days, the specific diagnosis must be reviewed and the sensitivity of the organism investigated. *Bacillus coli* cystitis is usually controlled by the sulphonamide group of drugs. If it is not, it behoves us to look for an underlying disease of the kidney or bladder. The only way of confirming the diagnosis of chronic meningococcal bacteriemia may be by the control of the disease by sulphapyridine, for it is extremely difficult to obtain the organism in blood culture.

The facilities for laboratory and radiological confirmation of diagnosis are becoming more and more available to the general practitioner. All over the country he has ready access to the Public Health Laboratory Service, and in many places the facilities of a hæmatological and biochemical laboratory and X-ray department are now at his service.

The ability of the general practitioner of Medicine to make a diagnosis and then set out to prove it or have it disproved is particularly important in those suffering from functional disease. For if the general practitioner makes a firm diagnosis and this is proved by hospital investigation and consultation, the patient is well on the road to rational therapy, whilst, on the other hand, if the general practitioner expresses doubt in the early stages, it is unlikely that consultant opinion will ever really remove it from the patient's mind.

Diagnosis of the patient means, to the general practitioner, an appreciation of the pathological process from which he is suffering, a knowledge of the environmental stress to which he is exposed, and an assessment of his personality.

[*November* 19, 1952]

DISCUSSION ON PEPTIC ULCERATION

Dr. Margarethe Mautner: It is in the hope that the scattered observations of other general practitioners may help to throw some light into the darker corners of this field that I propose to put before you some of the problems which have arisen in my practice.

A woman doctor's practice naturally includes a much larger number of female than male patients. Our practice—my partner is also a woman—is approximately 25% male and 75% female, but of the males a considerable number are children and therefore not subject to peptic ulcers. Nevertheless, about two-thirds of our ulcer cases occurred in male patients.

The local cottage hospital is staffed largely by general practitioners. With the help of a radiologist and a pathologist I can have my cases investigated without referring them first to an Out-Patient department. They are often admitted after only a short waiting period when I can control their in-patient treatment myself in consultation with the visiting physician or surgeon, and follow them up subsequently in the surgery or in their own homes.

The recent report of the Medical Research Council on "Occupational Factors in the Ætiology of Gastric and Duodenal Ulcers" (Doll and Avery, 1951) estimates that peptic ulceration accounts for thirty-three days sickness absence per annum per 100 men employed, and out of a population of nearly 43,000,000 in England and Wales it is stated that nearly 1,500,000 have or have had a peptic ulcer. This report also points out that the actual incidence in the general public is probably appreciably higher than that estimated. It is likely that a number are missed because they present themselves to

us with atypical symptoms; e.g. Mrs. L. I. S. living in a home for old people; she had been under treatment for some years for cardiac asthma and other symptoms of incipient heart failure. When she started complaining of abdominal pain and loss of weight, I referred her to a near-by hospital for investigation suspecting a new growth of the colon; a barium enema showed diverticulitis which seemed enough to account for her symptoms especially as she had somewhat independent views about diet, refusing to eat anything one day and consuming several pounds of raw pears the next. However, she suddenly had a hæmatemesis and profuse melæna, and post-mortem examination showed a large ulcer. Large numbers are also missed unless some catastrophe occurs because they are treating themselves with one or other of the popular brands of stomach powder and various fancy diets (one of the local chemists informed me recently that he sells approximately the same amount of popular stomach powders as he dispenses on N.H.S. prescriptions). One woman, because she did not like doctors, had been living for some time on a diet consisting largely of water-cress sandwiches. The friends of another patient tried to persuade him that repeated small doses of whisky were good treatment for his symptoms. As he found this rather expensive he did not persevere with it very long. Both these patients developed a sharp hæmorrhage which ultimately forced them to seek professional advice.

Early ulcer cases are not infrequently labelled nervous dyspepsia. The difficulty here is not only that the gastro-intestinal symptoms are atypical, but that they are often mixed up with all sorts of other symptoms and it is sometimes almost impossible to separate the so-called functional from the organic. It is not practicable to submit every patient with, say, two attacks of dyspepsia in three months lasting a week at a time to an X-ray examination, a test-meal and an occult blood test. I try to review occasionally the labels which have become attached to the chronic habitués of my waiting room as Dr. Simpson so aptly advised (*see* p. 353). In this connexion I should like to give you some details of a case, whom I saw first while he was on leave towards the end of the war. He was a diffident nervous type of man with a highly-strung, garrulous wife. He gave a history of bouts of epigastric pain lasting about a week every three or four months; the pain started three to four hours after his main meals, was sometimes relieved by vomiting but never troubled him at night. He was smoking 20–30 cigarettes a day. Various investigations while in the Army had given negative results and his symptoms had improved after taking "nerve tablets" given him by the M.O. After his discharge from the Army he had a number of short attacks of indigestion lasting a few days at a time generally relieved by pulv. magnes. trisilic. co. and phenobarbitone. Admission to hospital in 1948 showed some cicatrization of the duodenal cap, ? from an old ulcer, but no active ulcer and a hyperchlorhydria. After discharge from hospital he was comparatively free from symptoms for a couple of months, then the trouble started again, a week or two at a time. In 1950 a barium meal showed a definite duodenal ulcer. I had him in hospital for about two months and with rest, belladonna, phenobarbitone and magnesium trisilicate his symptoms disappeared and the ulcer healed. A few months later the trouble started again and in 1951 a chronic duodenal ulcer was found at operation and a partial gastrectomy performed: he has been free from symptoms since. The problems presented by this case are; how should this man have been treated in the first place? Did he have an ulcer when his symptoms first started, though the investigations did not show it? If he had, should gastrectomy have been advised sooner ? If the early symptoms were not due to an ulcer, could anything have been done to prevent one from developing?

So much for the difficulties of diagnosis. Now for some remarks on treatment. Many patients have done very well on routine medical treatment, almost always in hospital, and have subsequently enjoyed several years of freedom from symptoms, sometimes on a restricted diet, sometimes returning to full diet.

Whether the rapid cessation of symptoms after admission to hospital is due to the bed-rest or the dieting or the withdrawal from domestic or occupational strain I am not prepared to say. It is difficult also to estimate how much a cure ascribed to medical or surgical treatment may be partly due to extraneous causes. Thus L. S., a commercial traveller, had a melæna in 1940 and had been in and out of hospital for medical treatment. He subsequently had a gastro-enterostomy in 1945 and has been free from symptoms since; but for years previously he had been worrying about his wife suffering from pulmonary tuberculosis and about the possibility of losing his job after each spell in hospital. Soon after his operation his wife died and he has since got married again, so his worries have considerably diminished.

Another of my patients, J. F., is a hairdresser by trade and very deaf; after a long history of recurrent ulcers and several attacks of hæmatemesis treated medically he has now been clear for two years—in fact since he has been using a hearing aid. Is this merely a coincidence or is it due to the relief of the strain of trying to hear? There is no doubt that many patients suffering from ulcer-type dyspepsia are comparatively free from symptoms when relaxing on holiday.

Most of my cases of duodenal ulcer treated by partial gastrectomy have done very well, though I still feel that it is a terribly drastic form of treatment and what the late sequelæ may be nobody can yet say. The story of a patient whom I first saw about twenty years ago may be of interest in this connexion. I. S., a school-teacher aged 37, gave a history of having had a duodenal ulcer in her early twenties with severe pain and vomiting treated for some years as nervous dyspepsia and ultimately

cured by operation when she was 24. I took it some form of gastro-enterostomy had been performed as X-rays showed extremely rapid emptying of the stomach. She was subject to attacks of faintness associated with vasomotor disturbances which tended to occur when she was extra busy but with no great regularity. They were obviously a great nuisance to her and a puzzle to me. I had not at that time come across the "dumping" syndrome which follows some gastrectomies and which has received much attention recently, but I have no doubt her symptoms were similar in origin and partly due to a transient hypoglycæmia. They ultimately responded to glucose between meals and Bellergal tablets (containing belladonna, ergot and luminal), and gradually diminished in frequency. She was also subject to bouts of colitis often lasting for weeks on end.

Recently various workers have advocated a full diet for ulcer cases, stating that provided the patient does not rush his meals it does not matter what he eats. Though I am willing to concede the importance of peaceful and leisurely meals I do not know what the man quoted above with the garrulous wife is going to do about it, nor the people whose work compels them to take hurried meals in rowdy canteens.

To revert once more to the occupational incidence of ulcers, there are large numbers of transport workers, both bus and railway, living in my neighbourhood, but I have not found that an undue proportion of these suffer from ulcers.

REFERENCE

DOLL, W. R. S., and AVERY, F. A. (1951) *Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 276.

Dr. M. E. Shaw: I shall discuss the problem from the point of view of the help that the hospital physician can give to the general practitioner.

There is first of all the question of the various investigations which the hospital can carry out. One advantage which the consultant has in his out-patient clinic is that he has more time for history taking and may therefore be able to get a rather more detailed history than has been possible in a busy surgery.

In my experience the commonest mistakes in history taking are caused by the patients' difficulty in finding words to express their sensations, with the result that they use words which mean one thing to them and another to the doctor. For example the word vomiting is frequently used when nothing more than a slight regurgitation is meant. Even the word pain is sometimes used by a patient when only a mild discomfort is actually felt. In the hospital clinics these difficulties can often be sorted out and a full and detailed history may put a rather different complexion on the clinical diagnosis.

It is generally appreciated that there is a constitutional factor in peptic ulcer, and some twenty-five years ago George Draper in New York put this on a firm basis by his anthropometric investigation of patients with peptic ulcers. As a result of this he described what he called the "Ulcer Race" and the three most striking anatomical features of this race were a high palate with long incisor teeth, a wide angled jaw and a narrow epigastric angle. It is true that this type of person is the one most frequently affected by the peptic ulcer, but the broad thick-set type, which is more liable to gall-bladder disease, is not entirely immune. The former is obviously the type most prone to mental worry.

In the clinical examination the situation of the pain and of any tenderness are the important points. Peptic ulcer pain is rarely in the lower abdomen and I frequently start my questioning of the patient by asking if the pain is "above or below the navel". If below it is unlikely to be due to an ulcer although one could not absolutely exclude the diagnosis on this ground. Tenderness and guarding are more frequently to the right in duodenal ulcer and central, or to the left, in gastric ulcer.

The first problem for the hospital physician is to decide whether or not X-ray is indicated. I see no reason for doing a barium meal on young patients who have a really typical peptic ulcer history. Whether the X-ray shows an ulcer or fails to do so the patient will need ulcer treatment. I think most hospital physicians appreciate, as does the general practitioner, that one of the factors in favour of an X-ray is the psychological effect it will have on the patient. Nevertheless, there remains a large number of cases in whom straightforward treatment without X-ray is all that is required.

Of the other special investigations which are employed in hospital the test meal is used less and less as an out-patient procedure and the occult blood test is mainly used when anæmia is suspected or revealed by a blood count. Gastroscopy certainly has a place in the investigation of painful dyspepsia and may reveal a shallow ulcer or erosion which is not detectable on X-ray.

Having decided that an ulcer is present the next problem is whether to recommend admission or domiciliary treatment. This resolves itself as often as not into a problem of social medicine rather than clinical medicine. Our psychiatric colleagues impress upon us the importance of anxiety and worry in the ætiology of peptic ulcer. We have therefore to decide whether admission to hospital will allay or increase this factor. We have also to consider whether the home conditions make adequate treatment possible. As a rough generalization I would say that there are two groups who practically always require admission; firstly the bachelor living in lodgings, and secondly the married woman, who can never get away from her domestic cares unless admitted to hospital. In all these problems the hospital almoner is of the greatest possible help and, whether the patient is to be admitted or not, the almoner can do much to assist in the general management of the case.

Home treatment will of course have to consist of the two-hourly milk feeds with an antacid such as Aludrox or magnesium trisilicate. The other drug which has long been, and still is, widely used is belladonna (or atropine). Quite recently a combination of dried milk and alkali has been put on the market under the name of "Nulacin". These are dissolved in the mouth and, if taken sufficiently frequently, should produce a similar effect to the gastric drip, a treatment which can only be carried out in hospital. This latter treatment is the principal advance of the last ten years. Opinions differ as to when it should be used. I do not use it as a routine but confine it to two groups of patients, those whose ulcers do not heal on two-hourly milk feeds and those who get continual pain which can be relieved by no other treatment.

Nearly all patients will need some form of sedative and in selected cases the help of a psychiatrist may be sought. I do not hold the view that nothing but psychiatric treatment is needed. Whatever the psychological factors, the ulcer is an organic lesion and acid gastric juice is obviously not a good dressing for an ulcer. Acid secretion cannot be controlled by psychiatric treatment and therefore the customary regime will also be necessary.

In cases whose stay in hospital is prolonged some form of occupational or diversional therapy is of great assistance.

Opinions vary as to the effect of tobacco and alcohol. One has to weigh up the result of withdrawing either or both of these in each individual case. It may in some cases do more harm than good to forbid tobacco and, where this is the case, smoking should certainly be confined strictly to after meals. The harm done by both tobacco and alcohol is mainly the stimulus it gives to secretion on an empty stomach. Although I am sure that alcohol is best avoided, it will do less harm if taken diluted and with meals.

The indications for surgery remain the same as they have been for many years, namely, the failure of adequate medical treatment. I would, however, emphasize that the medical treatment must have been *adequate*. Too many patients are still referred to surgeons because medical treatment is said to have failed when, in fact, the medical treatment has been no more than medicine and a very slightly modified diet.

It is now by no means uncommon to operate on patients on account of hæmorrhage and certainly in the older age groups this measure may well be life saving. It does, however, require considerable judgment to decide in which case, and just exactly when, surgery is indicated.

In uncomplicated peptic ulcer in the younger age groups operation must be postponed until one is satisfied that repeated trials of medical treatment, carried out under the best possible conditions, and really conscientious after-treatment, have failed to secure a permanent cure.

Gastrectomy is now almost universally carried out, and in good hands this is a most satisfactory procedure. There is a small proportion of patients who are no better, and sometimes even rather worse, after operation. It is because of this small minority that one is reluctant to advise early surgery. A good deal has been written recently on the operation of vagotomy but I think the consensus of surgical opinion is that it is not a satisfactory answer to the question of peptic ulceration, except perhaps for the occasional anastomotic ulcer which may develop after gastrectomy.

[*December* 17, 1952]

DISCUSSION ON FITNESS TO DRIVE A VEHICLE

Dr. A. B. Davies (Police Surgeon, Walsall): *The Examination of the Drunk-in-Charge.*

In recent years and particularly in association with the vast increase of road traffic, drunkenness has assumed tremendous medico-legal importance. The medical examiner has a dual responsibility, one to the public and those who administer the law, and the other to the individual whose condition requires investigation. The consumption of alcohol, even in small quantities, affects the higher cerebral centres and the powers of judgment, and also slows down reaction-time. These effects alone, arising from quite a small intake, undoubtedly cause or contribute to many road accidents and cause avoidable loss of life, serious injury and material damage. When taken in greater quantity alcohol produces signs and symptoms obvious both to Police Officers and to lay witnesses. There comes a point at which the scientifically trained, medical examiner is expected to give a fair and reasonable opinion as to fitness to drive due to the effects of alcohol. The occurrence of constitutional disease, the taking of drugs from habit or in treatment, the effects of injury, shock and emotion may complicate the picture and make an accurate decision difficult. The penalties on conviction are heavy, including fines, imprisonment, loss of the driving-licence, on which some defendants depend for their living.

Again, unfortunately, there is not, and cannot be, any legal definition of drunkenness for the purposes of this offence. The Police Surgeon therefore has to form his opinion as to whether the defendant is "under the effects of alcohol to such an extent as to render him incapable of executing safely the occupation on which he was engaged at the material time". This definition covers all circumstances in which an opinion is necessary. It is essential, however, to ascertain whether the condition found is due to alcohol alone or whether it is wholly or partially due to pathological or other conditions, irrespective of the amount of alcohol consumed. Not only is it essential to be scrupulously fair to the defendant but the medical witness must be prepared to withstand a most detailed and withering cross-examination when the case is heard in court. I can think of nothing worse than an examining surgeon having to admit that he had not considered some particular alternative diagnosis or had not conducted some special examination which might be relevant. Even if he avoids this pitfall he must be prepared to justify every observation, comment or conclusion made. In view of what has already been said, and also of other difficulties to which I shall refer, it is obvious that there is no more difficult examination to undertake than the "Examination of the Drunk-in-Charge". It follows, therefore, that the examination should be most thorough and comprehensive, devoted at least equally to the consideration and possible elimination of alternative causes for the patient's condition.

I have now been Police Surgeon (part-time) to an important County Borough for seventeen years by appointment and about eight more years by deputy. During this time there has been the opportunity of examining more than a thousand individuals in various degrees of drunkenness and over three hundred have been examined under the accusation of being "drunk-in-charge". Most of these charges of course relate to being in charge of motor vehicles, but small numbers apply to being in charge of horses, bicycles and other forms of transport. I made up my mind from the beginning that I would not be bound by traditional custom and routine, but would devise and evolve my own technique, paying strict regard to scrupulous fair play and would not employ any test with which I might find difficulty myself. Thus, I have never used "tongue-twisters", walking a chalked line or acrobatic performances of any kind. I have tried to draw fair deductions from using simple functional tests of conventional type as used in ordinary clinical methods.

I have found that police officers have readily fallen in with any procedure I adopted and always accepted my certified opinion without question. By this I mean that, even if police and lay evidence has been strongly against the defendant no prosecution has taken place without supporting medical opinion. I mention this because there is nothing to prevent the police from doing so, and it is actually done in some places even if the medical evidence is in support of the defendant. Where this is done a specimen of urine obtained during the examination is afterwards sent to a laboratory and the findings, as regards alcohol content may support the police view. Although this plan is adopted with legal authority in Scandinavia, the ethics of applying it in England without consent, and in any case if a negative medical opinion has been found, do not appeal to me.

I find that it is seldom possible to give an accurate opinion on an examination of less than forty-five minutes.

I think the best way to cover the ground and deal with present-day problems is to take an imaginary case and go through it from the beginning to the end. It seems to me that everything is in favour of the defence (and rightly so). I have seldom seen or heard of a conviction being made unjustly, although of course some decisions are reversed on appeal. This circumstance in itself (the right of appeal) is another safeguard for the accused.

Only a minority of motorists "under the influence" are ever brought in. Some are lucky in avoiding accidents and others are never seen. The condition is only brought to light by the occurrence of an accident, the observation of grossly abnormal driving or behaviour associated with driving. The constable or layman forms a suspicion which is generally confirmed by another police officer before the driver is brought in to the Police Office. The officer in charge, a sergeant, has to satisfy himself before summoning the inspector who has overall charge of the "watch". Only if these officers have reasonable suspicions, is the attendance of the Police Surgeon requested. From this moment "Time" is very important and every material event must be related to time. The earlier the medical examination, the more accurate the opinion in relation to the offence at the material time. The Police Surgeon should normally arrive within half an hour of the arrest. His actual time of arrival must be noted. Observation of the accused by the surgeon commences forthwith. The Inspector has generally already told the accused that the Police Surgeon has been asked to attend and why. It is proper for the Inspector to inform the defendant at once that he has the right to have his own doctor present as well. In my experience the police always give the accused every facility in obtaining clinical and legal aid.

The first thing the Police Surgeon must do is to tell the accused who he is, why he has been asked to attend, and to ask for permission to conduct the examination. It is an assault for the Police Surgeon to examine without consent. If consent is refused or qualified, then the doctor should make careful note of everything that is said and write down observations of demeanour, and such clinical notes as are possible without submitting the accused to physical test. Sometimes permission is withheld until the arrival of the patient's own doctor. Notes and observations should be made during the waiting

period. If the patient's own doctor is not available or refuses to come, then a local list of available doctors should be supplied for the defendant to inspect and from which to make a selection. Often much time is lost in applying to numbers of doctors. The greater the delay the less valuable is the second doctor's opinion likely to be. During the waiting period, especially if unduly prolonged, observations noted by the Police Surgeon are likely to be of supreme importance at the hearing. Ultimately there comes a time when the patient's own doctor or some other selected doctor arrives, or after the flux of time it is obvious that no other doctor is likely to come. Now, either the examination goes on with consent, or it does not take place at all. In the latter case the Police Surgeon is justified in forming an opinion on prolonged observation of demeanour, &c. In rejecting or postponing examination the accused is not only excluding the elicitation of evidence against him, but also of the demonstration of facts and evidence in his favour. Benches and juries often regard the refusal of consent as a guilty desire to exclude damning evidence. If consent to medical examination is withheld without qualification then there is no point in the surgeon staying and he should record the fact of request to examine and refusal. In such cases there may, of course, be a hearing on lay and police evidence alone.

The Police Surgeon should also advise the defendant that he can consult his solicitor if he wishes. In actual practice this privilege is seldom used. The Police, however, give every assistance in endeavouring to obtain the services of the accused's doctor and lawyer. It is plain, of course, that the financial responsibility in both cases falls on the accused. It is no part of the responsibility of the police to pay for the lawyer or second doctor. It is necessary to remind some defendants that there is no obligation on the part of his "State" doctor to attend on request. It is no part of his terms of service. As regards solicitors, patients do not readily invite them. In any case they are seldom accessible in the night and rarely accept inconvenient calls as doctors do. However, a number do give advice on the telephone and a few actually come.

As regards the value of examination to the accused I wish to say that I have rejected certification in 40% of cases submitted to me. This shows that some at least have derived benefit from medical examination. At the same time it is only fair to the police to say that all the cases examined were proper cases for examination. The cases rejected were either border-line or suffering from some other condition as well as drink.

If the second doctor comes on request I generally ask him to witness my own examination and then apply his own or supplementary tests. If the patient wishes for the second examination to take place *in camera* it is of course allowed. Sometimes the patient has agreed to examination by the Police Surgeon alone, being overconfident of the findings. When he finds that the opinion is unexpected he *then* asks for another doctor. This is annoying to the Police Surgeon who is often asked to be present later when the second doctor arrives. However, valuable time has in any case been lost to the defence. If two or more hours have elapsed then the patient's condition will have improved. The second doctor in cross-examination is bound to admit that the opinion based on the first examination is likely to be the more accurate.

Privacy.—The actual examination should be conducted under maximum conditions of privacy, i.e. not in the busy Charge Office. It is desirable to have a reasonably large, warm and well-illuminated room. During the journey to such a room (say the Magistrates' Room) the doctor should follow the accused so that he can observe the gait and manner of going through doorways, turning bends and going up or down steps, when these hazards are available.

Within the room are the doctor and the accused. In addition I always allow the presence of one police officer only (and the other doctor if attending). The presence of any police officer at all has been much criticized, especially by the Scottish Judges. In my opinion the presence of one high-ranking officer is essential for the following reasons, viz.:

(1) The defendant is in custody and the doctor is not a policeman.

(2) For the protection of the doctor. Twice I have actually been assaulted during the conduct of the examination.

(3) For the confirmation, if necessary, that certain tests were actually conducted and that certain things were said. (Some defendants during the trial deny that some tests were done and repudiate statements ascribed to them.) It is only under these conditions that the police-officer is allowed to give evidence of what transpires during the examination. Otherwise, all the observations, comments and opinions are the property of the doctor alone.

(4) To lend necessary assistance, e.g. to fetch writing pad, newspaper or other matter for the reading test, to take the defendant to the toilet, &c.

I am sure that the above reasons fully justify the presence of one high-ranking officer. If these valid reasons had been given to the Scottish Judges I am sure they would not have made such strong adverse comments. I have already referred to the patient's right to have his own doctor and solicitor present if he wishes. When other doctors have been present I have never known them object to the presence of the police-inspector.

Writing test.—I generally ask for a written consent. This is not only proof of consent but also a good specimen of handwriting taken at an early time. The actual wording I make standard and is as follows: "I am willing to be examined by Dr. So-and-so, the Police Surgeon", signed and dated. I first state the actual passage at normal conversational speed and then dictate slowly at dictation speed, spelling words where necessary. I allow the accused to sit down, at a table and in a good light, using lined paper and writing with pen or pencil as he wishes. The handwriting by itself, of course, is of little value. Some are illiterate, others have poor penmanship and again most people have intrinsic peculiarities of pattern and style. Comparison can only be fairly made by testing the same script at a later date. However, gross defects are often seen, especially in spelling and in spite of slowly dictated spelling. Syllables, letters and strokes are often repeated. The letters N, M, and W particularly cause difficulty by the production of excess up-and-down strokes. Sometimes gross inco-ordination is seen. The date frequently creates difficulty, especially in the early hours of the morning. Estimates of time are asked. Gross errors are sometimes found in the replies, but unless checked many candidates immediately look at the wrist-watch and invalidate the test.

General observations.—The smell of alcohol in the breath is usually obvious as soon as one enters the room. It should be noted although, of course, it is no index of the amount consumed. Sometimes there have been attempts to mask the odour. Peppermint is viewed with suspicion and is noted. It is, however, seldom successful in completely masking the smell of intoxicants. In recent times the use of the deodorants (chlorophyll) has undoubtedly succeeded in some cases. Often the breath is rancid and stale. The tongue and throat are generally red and dry. It must be remembered that an injured or sick man may have been given "a nip" by some well-meaning bystander.

The skin is usually flushed, the upper eyelids are heavy, the whites of the eyes muddy and bloodshot, the pupils dilated in varying degrees and with varying responses to light. In the alcoholic state the response is generally poor and sluggish, with frequent hippus reaction (alternate contraction and dilatation). In heavy drinking there is often no response to light at all.

There may be evidence of injury, wounds or blood stains. The clothing is examined. The dress may be untidy, e.g. the coat or fly buttons fastened in the wrong holes, the tie loose and at the side of the neck. There may be mud-stains, dust-marks, tears and cuts, all of which may be material to the condition and circumstances.

There may be vomiting, actually during the examination, or the vomit staining the clothing. The vomit smells strongly of drink.

General demeanour.—Alcohol affects different people in different ways. Sometimes the demeanour of the same individual changes during examination. Some are abusive and offensive, others hilarious and facetious, a few are maudlin and depressed. Moods may change from full co-operation to hostility with abuse. Some are noisy and garrulous. Almost without exception they are sure they have done well in their tests. It is this confidence which makes some of them say at the beginning: "I don't need any other doctor, I'll be satisfied with you."

Pulse.—In my experience the pulse-rate is always increased and this increase is substantially maintained during the examination. The actual rate is recorded both at the beginning and end of the examination. The respiration rate is also recorded—and this also is usually increased. As a routine the temperature is taken to exclude febrile conditions. The blood pressure is also recorded.

Physical examination.—A complete examination follows with particular reference to the heart, lungs and nervous system. Negative findings are just as valuable in evidence as positive, and should be recorded in view of the possibility of other explanations being put up by the defence. I always ask about the personal medical history, when last a doctor was consulted and for what purpose, whether the accused had been in the forces and what was the discharge category. The occupation is important and also the acceptance or rejection for life insurance. I then ask if there is any complaint of present illness or whether any injury has been received in the present circumstances.

This part of the examination and enquiry is particularly directed to the existence of alternative causes for the conditions found. A thorough physical examination shows the presence of needle punctures as in diabetes and drug-taking. The later urine examination may disclose glycosuria, albuminuria in uræmia, &c., while ketones may also be present. A diseased heart, hypertension, asthma and bronchitis, anæmia, mental states, organic nervous disease, pyrexia, &c., can all be detected by efficient examination assisted by pointed questions. The writer has met with all these and other conditions in the routine examination. Full allowance has to be made for the effects of these conditions when present, even amounting to their acceptance as being fully responsible for the incapacity in driving. The taking of tablets and drugs for the treatment of disease has been sometimes put up by the defence at the trial. I have in this respect met with opiates, belladonna (and other anti-asthmatic and anti-spasmodic drugs), the barbiturates, antihistamines, and alkalis to suggest alkalosis in the treatment of gastric ulcer. The effect of head injuries is often suggested, e.g. concussion—and this, of course, may actually be present. The writer has met several cases of "punch-drunkenness". This occurs in ex-pugilists who have had frequent battering to the head. In this state often one half-pint only will convert the subject into a raving and violent maniac for a short period. The effects on

such a driver may well be imagined. Major and minor epilepsy are occasionally suggested but the admission of these and some other conditions presupposes that a false declaration has been made on the application for driving licence. The use of this defence inevitably means cancellation of driving licence and maybe prosecution for wrong declaration. Malaria may produce some of the signs. The effects possibly of petrol and exhaust fumes must also be borne in mind. Perhaps the commonest suggestion by defences is "shock"—a term vaguely applied and which may mean either surgical or emotional shock. Another loose term applied is "black-out".

The eyes.—In addition to the preliminary observations already discussed there is the question of impaired vision. Are glasses normally worn? Were they being worn at the time of the offence? Has the patient the glasses with him now, either being worn or in his pocket? Rough tests should be made for distance as well as taking the reading test for near vision, allowing the patient to use his glasses if he normally uses them. Examination of the optic discs by ophthalmoscope may show retinitis, arteriosclerosis, choked disc, &c.

The writer has met cases of fracture of the skull with extradural hæmorrhage, and also cases of subarachnoid hæmorrhage.

Co-ordination.—Good co-ordination and reaction-time are of very great importance. Opinions on these will have been formed in relation to many of the tests already considered. Rapid action in an emergency depends on efficient use of the senses, particularly the eyes and the muscles of the hands and feet. Balance is important. Romberg's test is conducted and tests are made for tremors. The muscle reflexes are tested. The gait should be further observed in walking across the full length of the room, turning round and walking back. All kinds of abnormal gait have been seen from the rolling, lurching variety as seen on a ship deck in heavy seas to the stamping, military exaggeration of the over-confident. Reeling and lurching is common on turning and in going through a doorway often there is brushing against the lintels. Picking up a match is an excellent test of co-ordination. Apart from failures one sees groping and fumbling, scraping of fingers along the floor and often an indirect approach as against the normal speedy direct method. I ask the patient to dress himself after examination. Tying the shoe-laces, fastening the shirt and trouser buttons are excellent tests of co-ordination. I have already referred to the handwriting.

Speech and reading.—Ample opportunity of noting abnormal speech will already have been obtained. Hiccups and yawning may have been noted. If there is yawning the time of the last sleep should be ascertained. The reading should be tested in a good light and a daily newspaper used. I always ask the patient to make his own selection as it is sometimes alleged that a specially difficult selection has been made. The parts read should be marked plainly by crosses at the corners for production as an exhibit in court. Allowance is made for illiteracy. The commonest faults are lisping and slurring, but there are frequent repetitions of words and syllables, sometimes the omission of words or whole lines and at other times the insertion of extra words. As regards the speech, allowance must be made for racial and dialectical peculiarities.

Old injuries.—Scars of former injuries and deformities of limbs and joints should be noted as they may have some relevance in relation to some tests.

The memory test.—This is one of the best tests of mental alertness and efficient cerebration. Some objection was made to it by the Scottish Judges but, fairly conducted, it is a most useful and important test. If the accused makes a good response it is in his favour. It is quite wrong for the examiner to ask any leading questions such as how much drink has been taken. I first ask the accused if he is willing to co-operate in a memory test, the purpose of which is to test his mental alertness and brain efficiency. If he agrees, I then ask him to give an account of his movements and actions during the preceding six hours. I also tell him that he need not take part in the test if he does not wish and that he need not say anything he does not wish. In spite of this warning many individuals make most damning admissions about the drink they have consumed. In general one finds that there is an early detailed report of great accuracy. As the time of maximum intoxication approaches the account becomes vague, devoid of detail and frequently there is a complete hiatus. If there has been an accident there is generally little knowledge of it or of the circumstances leading up to it. Often, soon after an accident there is renewed alertness of memory. Without putting any further questions I read the statement to the accused. He usually agrees, but may make additions or amendments.

State of weather, &c.—It is wise to make a note of the state of the weather at the time of the examination. The case may not be heard for months and recollections may then not be clear. Conditions such as fog, snow, rain, extreme cold or excessive heat may be relevant to the case.

The accused is asked if he is willing to pass a specimen of urine. Sometimes this has been done before the arrival of the doctor. A few people object but most defendants are only too glad to oblige. If willing, he is taken to a lavatory and is offered a clean vessel in which to pass urine. Any specimen collected is measured and divided into three equal parts, one of which is offered to the accused or his doctor.

The clinical examination and period of observation is now finished, subject to possible supplementary tests by the accused's own doctor. On this examination and on the examination alone the opinion is formed. The examiner should never ask questions of the police as to circumstances leading to the arrest. Any such pre-information might unconsciously bias the opinion.

The opinion is entered in the Occurrence Book in the following form: "Date. Time. I have examined John Blank at the Borough Police Office and have formed the opinion that he is under the influence of alcohol to such an extent that he is incapable of exercising proper control of a motor vehicle. Signature." If a second doctor has been present he is asked to enter a note to the effect that he was present, but I advise him not to enter any opinion in writing.

At the earliest convenient time the urine specimen is examined. It may show albumin, sugar, acetone bodies or other abnormal contents. It may be that the discovery of such abnormalities may cause one to amend the opinion formed on clinical examination. In practice after careful examination and history-taking this seldom happens. Nevertheless it is necessary both in fairness to the accused and for the protection of the examiner.

Later speakers and technical experts will discuss the methods and value of alcohol investigations of the blood and urine. Evidence of laboratory findings, particularly when translated into the minimum quantity of alcohol present in the body, is most valuable corroborative evidence. I do not think that laboratory findings should be accepted alone, as is the case in Scandinavian countries. I have already said that the opinion as regards certification should be based on clinical examination and prolonged observation. I believe this to be fair. We have not yet reached the stage in this country when Police can take a motorist inside and subject him compulsorily to laboratory tests. Nevertheless the urine alcohol can give most valuable confirmatory information.

Apart from the smell of alcohol in the breath or vomit, and the finding of alcohol in the blood and urine, none of the other tests is by itself conclusive evidence of the consumption of alcohol. When giving evidence, therefore, it is important to give all the tests and the results thereof and to advise the court that the opinion is based on a very large number of observations and tests, due weight and consideration having been given to possible alternative causes and having regarded favourable responses as weighting the case in favour of the accused. It is better to give all the findings fully in "Evidence in Chief". It creates a bad impression in court if all the responses favourable to the defence have to be elicited and conceded in "Cross-examination". This may appear to take up the time of the court but is only fair to the defendant. If there is a plea of Guilty it is often only necessary to give the opinion and brief supporting evidence.

Every examiner is entitled to conduct his own examination in his own way, but in my experience the above technique has served me very well and I am convinced has formed the basis of fair and accurate opinions which have only very rarely been disturbed by the courts.

Dr. F. E. Camps: The role of the medical practitioner in connexion with the Road Traffic Act is primarily to decide whether the person is fit to be in charge of a motor vehicle.

This fact is, to some extent, lost sight of, so that the emphasis is placed upon the signs of being affected by alcohol, thereby neglecting the general physical examination which will detect the natural disease which may simulate or enhance those effects. That this is so in many cases of examination of people who are suspected of being under the influence of alcohol whilst in charge of a car can be easily shown by the constant reiteration in the witness box of an absence of a proper physical examination. Further, another thing which is lost sight of, is the fact that the time of the offence *is when the person is originally pulled up, not* when he is medically examined and much can happen in the interim period. Hence quite clearly the most important *evidence* as to whether the person's behaviour was abnormal is that showing abnormal behaviour. I would go so far as to suggest, in fact, that the average police officer is best able to decide whether an individual is affected by alcohol or not. On the other hand he is quite clearly not trained to establish whether a person is suffering from disease, which is the duty of the medical practitioner. Finally, there is the decision as to whether alcohol has been taken, which can be shown from the smell of the breath although this certainly does not indicate whether a lot or a little has been consumed. The chemist can help in this matter, for analysis of the blood or/and urine can, if properly carried out, with proper technique of collection, proper analytical method and properly experienced analyst, show the minimal quantity consumed but *no more*, for individuals vary in their reaction to alcohol. One may be affected by a single glass of sherry whilst others can tolerate several large whiskies without obvious effects.

The assessment of any individual suspected of being under the influence of alcohol seems to fall into three parts:

(1) The behaviour at the time of the incident and following it.

(2) Exclusion of disease of causing this.

(3) Proof of alcoholic intake which could cause it.

The medical man's opinion is of fundamental importance in respect of (2) for on some occasions he may find natural disease, such as gross hypertension, which can entirely account for the symptoms and behaviour, whilst in others the most difficult problem is of assessing how much of it is due to alcohol and how much due to disease. The decision of this will depend upon a *proper* clinical examination to exclude such things as diabetes and insulin, chronic cerebral contusion and the like. At the same time the various possible lines of defence must be considered such as carbon monoxide poisoning —Ménière's disease and so on.

In stressing the medical point of the examinations it may well be said that suitable doctors are not always available. For this we must blame ourselves for they have been driven to avoid such a duty to the community by fear of wasting much of their valuable time in Court, a wastage which is not always necessary, for a tactful word with the Clerk of the Court will often smooth the way and reveal when the case is likely to be heard. In the same way others avoid the task for fear of cross-examination, again a fear which should not occur with people whose evidence is fair and unbiased.

Mr. L. C. Nickolls (Director, Metropolitan Police Laboratory, New Scotland Yard) opened his contribution by saying that the opinions expressed were his own opinions and did not reflect in any way the official policy which was, of course, dictated by considerations outside his sphere. He pointed out that he was not a doctor himself, but that, having given evidence in many hundreds of cases of unfitness to drive, and having seen the reaction of the defence to the evidence given by so many medical men, he felt that there were several points that he would like to make from the point of view of an interested observer.

He said that originally the charge was one of being "drunk in charge of a carriage", but that under the Road Traffic Act this had been changed to being "under the influence of drink to such an extent as to be incapable of having proper control of a motor vehicle". While the new Act may have intended to decrease the ambiguity of the charge, it does not appear to have achieved its object. He recalled a case in which a man, who had never driven a motor vehicle, while under the influence of alcohol stole a vehicle and attempted to drive it, thereby driving into a tree. It appeared a difficult matter to decide whether the unfitness to drive was due to inability, or to the effect of alcohol.

He pointed out that originally the doctor was called in to satisfy the police and the Court that the condition of the accused man was not due to injury or disease, but was due to the effects of alcohol. It was, in those days, accepted that the police officer who arrested the man was the best judge as to his sobriety, but that the possibility of a defence of illness could not be overlooked. The doctor who is, of course, a valuable link in a chain of evidence, has recently tended to be more aware of the part played by his diagnosis of the degree of intoxication of an accused, and cases in which the speaker had been concerned have sometimes failed because some disability had been overlooked by the doctor in attendance. This is more particularly to be expected when the accused is so clearly under the influence of alcohol that it would appear obvious that he was unfit to drive through drink, irrespective of any other disability.

He was interested in the chemical examination of blood and urine in such cases. He pointed out that the scientist could never state the degree of intoxication of a person from the amount of alcohol consumed. Nevertheless the test was a valuable one. The scientist determined accurately the concentration of alcohol circulating in the blood or present in the urine and from this an accurate estimation of the amount of alcohol recently consumed can be given. This negatives a defence that only small amounts of alcohol have been consumed.

In cases which go to Quarter Sessions, in particular, the utmost strength is required by the prosecution, since juries are very reluctant to convict. In his experience, the amount of alcohol consumed was always a comparatively large amount, the figures actually "peak" at about 300 mg./100 ml. in the urine. This is because drivers consistently drive more and more badly up to this figure, but beyond this figure many of them cannot drive at all because they are in a state of sleep or coma. He drew attention to the necessity for excluding alcohol from all articles used for taking such tests, e.g. syringes should not be sterilized with alcohol. The skin should not be sterilized with alcohol, Dettol, ether or tinctures such as tincture of iodine. The containers should be clean and dry, and should preferably be new, unused containers.

Dr. Guy Daynes spoke in defence of the legal profession and their methods of cross-examination which had been criticized. There could be little doubt that these methods, even if they were embarrassing to some members of the medical profession, revealed the truth in most cases. Much might depend on the preparation of medical evidence; what might seem obvious to the medical man was not necessarily so to the judge and jury. Not many cases of "Drunk-in-charge" were acquitted in the absence of help from a second doctor called to examine the accused after the police surgeon. However unpleasant this task might be, it was a most important one; without this second opinion many an innocent man might have been convicted.

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Section of Anæsthetics

President—M. D. NOSWORTHY, M.A., M.D.

[*January* 2, 1953]

The Role of Carbon Dioxide in Anæsthesia [*Summary*]

By R. P. HARBORD, M.D., F.F.A. R.C.S., D.A., The Hon. S. PARNELL, B.Sc., and A. B. EASTWOOD, M.R.C.S, L.R.C.P., D.A.
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B. G. B. LUCAS, M.R.C.S., L.R.C.P., D.A., and E. H. MILNE, M.B., D.A.
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Dr. R. P. Harbord, Mr. S. Parnell and **Dr. A. B. Eastwood:** *Spontaneous pulmonary ventilation related to carbon dioxide elimination.*—The carbon dioxide content of gaseous mixtures from the depths of the lungs has been correlated with pulmonary ventilation during 35 relatively minor operations, mainly herniorrhaphies, performed under thiopentone anæsthesia with Flaxedil in all cases and with pethidine in 11.

Only oxygen was inhaled through a large sized cuffed endotracheal tube connected to a Waters' canister filled with fresh soda lime, and with the reservoir bag replaced by a bellows whose movements were recorded. This bellows was similar to the one described by Benson *et al.* (1951).

The subjects' ages varied between 22 and 63 years and were mainly between 30 and 50 years. During the period of observations the average dose of thiopentone was slightly over 1 gramme, and that of Flaxedil 114 mg. The dose of pethidine ranged from 25 to 100 mg. The aim was to maintain tidal volumes similar in extent, judged by bag movements, to what was frequently allowed by anæsthetists for this type of operation.

Blood loss was minimal but was not measured.

Gases were obtained during spontaneous breathing from the depths of the lungs by a rapid manual chest compression at the end of an expiration, and while the anæsthetic apparatus was temporarily cut off at the endotracheal mount, an evacuated gas sampling tube was opened through a rubber bung in the suction limb of a Cobb's adaptor. The forced expiratory volume was recorded. Blood samples were taken anaerobically from the radial artery at this time.

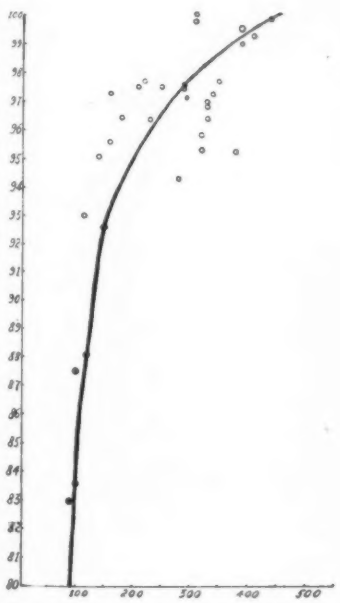


FIG. 1.—Abscissæ: percentage of original sample. Ordinates: volume displaced in millilitres.

The sampling process has been investigated to determine whether alveolar or dead space gases had been obtained. A model glass trachea was constructed, 2 cm. in diameter, fitted at one end with a rubber bag, which could be distended and then released to discharge a given volume of gases of a known carbon dioxide content. Through the upper end was passed a cuffed endotracheal tube with a Cobb's adaptor; the dead space, 110 ml., approximates to that of the sampling system of the average patient.

Because of the lack of respiratory data for the anæsthetized patient, the results have been related to existing values for the normal conscious subject at rest. For respiration rate the limits are from 14 to 18 per minute; for tidal volume, 350 to 500 ml. Hence the limits for minute volume are calculated to be from 4·9 to 9 litres per minute, and if the dead space is assumed to be 150 ml., the effective or alveolar minute volume limits lie between 2·8 and 6·3 litres per minute. The average tidal volume of patients was calculated from the arithmetical average of all the inspirations in the minute before sampling the lung gases. The carbon dioxide content of alveolar air in the normal subject at rest has been taken to vary between 4·7 and 6·4%.

RESULTS

Fig. 1 shows that when 140 ml. or more pass through the model trachea, previously containing air, 90% of the carbon dioxide content could be recovered at the Cobb's adaptor, and 95% when the volume exceeded 200 ml.

The duration of the whole sampling process in patients was less than 5 seconds in over 70% of the examples.

A comparison between the carbon dioxide tension in the lung gases and the calculated tension in arterial blood, practically simultaneously drawn, showed that an agreement of plus or minus 5 mm.Hg could be obtained in one-third of the examples, the remainder demonstrating a higher tension in the lung gases.

Fig. 2 shows the extent of pulmonary ventilation before sampling on 108 occasions, the extent of the forced exhalations and the carbon dioxide percentage of the samples.

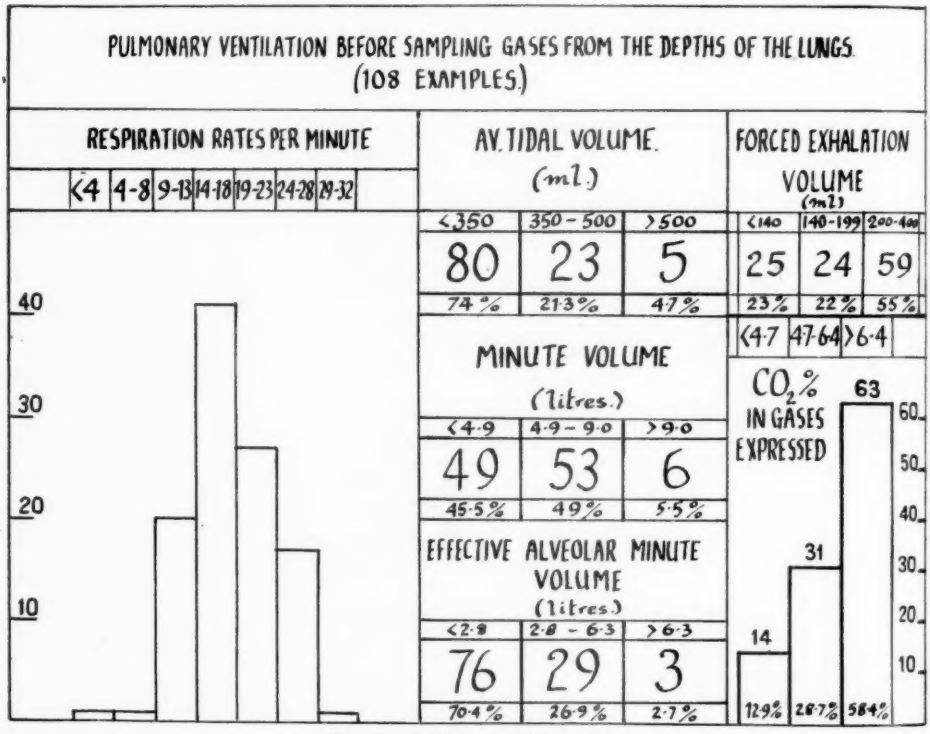


FIG. 2.—Table summarizing results.

The relation between the average tidal volume and the percentage of carbon dioxide in the lung gases is shown in Fig. 3, the examples being chosen for uniformity in respiratory pattern.

After respiratory depression one pattern showed a return to normality of tidal volume more rapidly than that of the carbon dioxide content of lung gases—changes of from 190–370 ml. of tidal volume corresponding with carbon dioxide percentage changes from 8·6 to 7·7%—measured during nineteen minutes of recovery of ventilation after extreme depression.

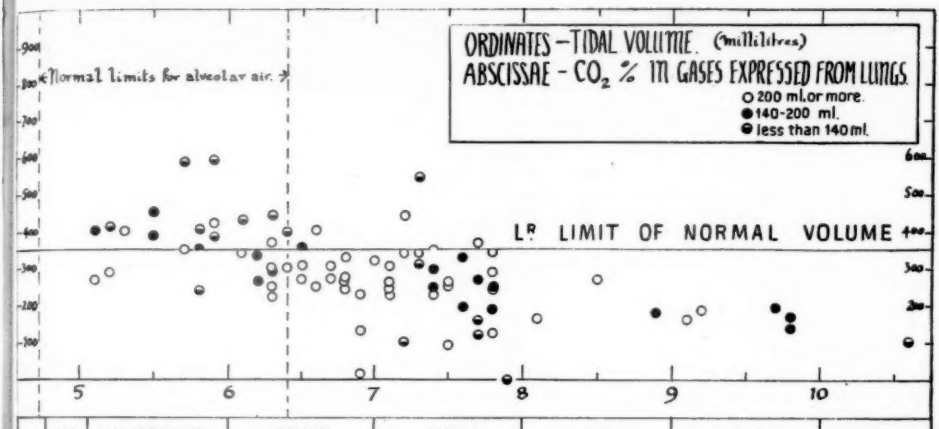
The longest period during which samples of the lung gases had values between 8 and 9% was nineteen minutes. All the patients recovered.

The classical signs of carbon dioxide excess were not observed although particular care was taken to observe changes in the facial colour and the state of the skin and the superficial vessels.

Bleeding from cut surfaces did not appear to be increased even when the carbon dioxide percentages in the lung gases were above the usual alveolar limits.

DISCUSSION

The results show that when the average tidal volume is between 350 and 500 ml., the percentage of carbon dioxide in the lung gases lies mainly within the limits found in the alveolar air in conscious subjects at rest.



NO	AV. TIDAL VOL	RANGE	MEAN	S.D.	C.V.	TOTAL
22	350–600	5·1 – 7·7	6·1	0·72	11·7 %	81
41	200–349	5·1 – 8·5	6·9	0·69	10·0 %	
18	0 – 200	6·9 – 10·6	8·3	1·06	13·3 %	

FIG. 3.—The distribution of carbon dioxide percentage in gases expressed from the lungs in relation to tidal volume.

Since the interval between the end of expiration in patients and the opening of the tonometer was generally less than 5 seconds, carbon dioxide accumulation during the sampling process was probably negligible as is indicated by the work of Dubois *et al.* (1952).

The experiment with a model trachea suggests that when more than 200 ml. are forced out from the lungs by a rapid chest compression, then the carbon dioxide content of the gases will be a slight underestimate of the alveolar value.

The reason for the difference between the calculated arterial carbon dioxide tension in the blood and the tension in the lung gases is not clear. This problem is the subject of a separate investigation.

Haldane and Priestley measured the tidal volume changes in conscious man breathing carbon dioxide mixtures, and found that when the alveolar carbon dioxide changed from 5·6 to 6·6%, the tidal volume increased from 673 to 2,104 ml.

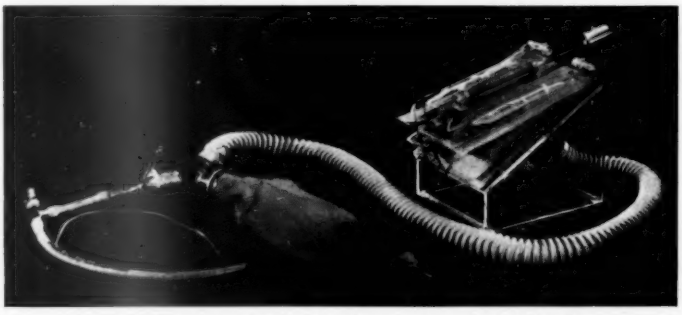


FIG. 4.—Apparatus for the visual measurement of tidal volume.

Using a method which slightly underestimates alveolar carbon dioxide it has been shown that when the gases from the depths of the lungs contained from 6·9 to 10·6% of carbon dioxide, the tidal volume varied between apnœa and 200 ml. Such is the order of change in the anæsthetized state.

Pulmonary ventilation should be assisted under anæsthesia when the tidal volume falls below 350 ml. An instrument for measuring tidal volume is described in the appendix.

Carbon dioxide excess is an insidious state in the unconscious subject and may persist when the tidal volume is above 350 ml. if the previous ventilation has been below normal.

Because patients have recovered despite high percentages of carbon dioxide (8–9%), in the gases from the depths of the lungs lasting for periods up to nineteen minutes, it does not follow that this state is one from which no harm will accrue. Clearly, more work is indicated to settle this point. It appears that where respiratory depression is allowed carbon dioxide will accumulate, probably more so than has generally been realized, and may even decide the issue unfavourably in gravely ill patients.

Appendix

A tidal volume recorder has been constructed on a similar principle to the one used for recording pulmonary ventilation but smaller and with a lever operating against a scale calibrated to each 100 ml., and supported on a plastic stand. The recorder may be attached to standard apparatus by a large bore 3-way tap as shown in Fig. 4.

Acknowledgment[1]

We wish to thank Mr. L. Byrom for his technical assistance in the laboratory, and also the surgeons of the United Leeds Hospitals for their co-operation. Our thanks are also due to Mr. H. R. Noltie of the Physiology Department (University of Leeds), for much valuable advice.

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[*This paper will be published in full elsewhere*]

Dr. B. G. B. Lucas and Dr. E. H. Milne: The role of carbon dioxide in anæsthesia cannot be discussed without a prior knowledge of the mechanisms which maintain the acid-base balance in the blood at a normal level in the conscious subject. The hydrogen-ion concentration depends on the ratio of free carbonic acid to that combined as bicarbonate and rapid alteration in the ratio may be effected by the "chloride shift" whereby more base is made available, and by the extreme sensitivity of the respiratory centre to changes in pH resulting in adjustments in ventilation and excretion of carbon dioxide via the lungs. During surgical operations the acid-base balance is disturbed because of the effect of the anæsthesia on the respiratory centre and on the dynamics of respiration; hence some degree of carbon dioxide retention occurs. Accordingly, the acid-base changes that occur during surgery have been studied by estimating the carbon dioxide tension in the circulating blood during operations. The carbon dioxide tension was calculated from measurements of the total carbon dioxide content and pH of the blood (Peters and Van Slyke, 1931). The carbon dioxide content was measured by a micro-volumetric method using capillary blood (Scholander and Roughton, 1943). The pH was recorded electrometrically with a potentiometer and glass electrode, the latter being incorporated in a special syringe into which blood was drawn anaerobically under mercury. To facilitate blood gas analysis anæsthesia was maintained with thiopentone or pethidine, with tubocurarine or Flaxedil for relaxation. All cases were intubated and the carbon dioxide absorption technique was used whenever controlled or assisted ventilation was performed. 159 cases have been investigated, 80 being for abdominal surgery, 62 for thoracic surgery and the remainder limb operations in which the effect of posture was deliberately studied.

In the series of abdominal cases operated on in the supine position there was always a rise of carbon dioxide tension if the patient was allowed to breathe by himself. If vigorous controlled ventilation was carried out from the start of the operation, the tension could be kept within normal limits, but only in the presence of a perfectly free airway. It was impossible to ventilate any patient adequately if he were in the Trendelenburg position, in spite of attempted overventilation. The effect of posture on ventilation was deliberately studied on 17 patients undergoing minor limb operations. In the Trendelenburg position the rise of carbon dioxide tension was found to be proportional to the degree of tilt. In the lateral position the carbon dioxide tension increased, particularly if the table were broken. In the thoracic cases the increased carbon dioxide tension due to the lateral position and to breaking the table rose further when the chest was opened because of the unavoidable inadequate ventilation, being most marked in operations where a lung was deliberately deflated, e.g. an oesophagectomy, or when a bronchial occluder was used (Fig. 1).

A number of effects were observed on the anæsthetized patient when there was a respiratory acidosis. The systolic blood pressure rose during major surgery, but fell abruptly immediately post-operatively

[1]Part of the expenses for this work was defrayed by the Association of Anæsthetists of Great Britain and Northern Ireland.

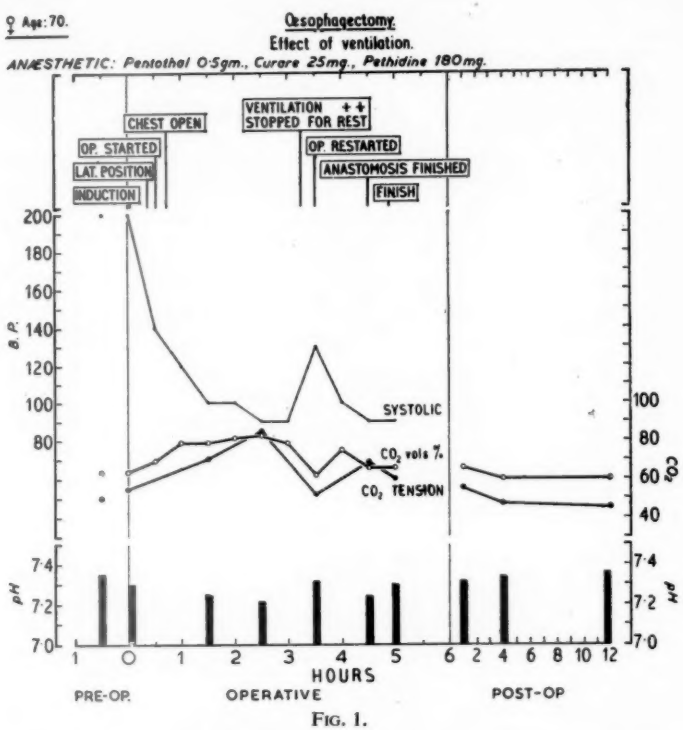

FIG. 1.

and was accompanied by signs of circulatory collapse. The dosage of thiopentone necessary to maintain an even plane of anæsthesia was increased. Operative reflexes were more active and recovery time delayed. Whether the delay in recovery was due to the increased amount of thiopentone used or to a diminished rate of breakdown of thiopentone in the body was not discovered. In upper abdominal surgery a respiratory acidosis was associated with hiccup.

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[*This paper will be published in full elsewhere.*]

Dr. Ronald Woolmer: Most anæsthetists are aware that carbon dioxide accumulation must be harmful, but the harm it causes is often not apparent, and the importance of avoiding underventilation is therefore not self-evident. We can very seldom say, with any confidence, that a patient's recovery has been prolonged or complicated because of carbon dioxide retention during anæsthesia. It would be a help to us all if we could be told that certain specific bad effects are causally related to carbon dioxide retention, so that they always appear when it has occurred, and never when it has not.

Dr. E. J. Moran Campbell: The functional dead space of an apparatus is not the same as its volume. The shape is important; where it contains an expanded portion gases can pass through in a stream without mixing with the main volume, thus reducing the dead space. A constriction can have a similar effect. In such circumstances the functional dead space also depends upon the volume rate of gas flow. Even with an apparatus consisting of tubing of uniform bore the functional dead space is probably always less than the volume.

When considering the effect of an apparatus on the ventilatory exchanges, in addition to dead space the resistance must be taken into account at all levels of ventilation occurring under the conditions in which it is used. Cain and Otis (1949, *J. Aviat. Med.*, **20**, 149) have shown that added resistance to respiration causes a rise in alveolar pCO_2. The resistances they used are probably much greater than those occurring in anæsthetic machines. Their subjects, however, were conscious and not curarized. During anæsthesia lower levels of resistance may suffice to cause CO_2 retention.

It is instructive to work out pH changes in terms of actual hydrogen-ion concentration. A change of 0·3 of a pH unit may mean a halving or a doubling in hydrogen-ion concentration. A rise of 0·3–0·4 in the pH has been recorded during anæsthesia (Dundee, J. W., 1952, *Brit. med. J.*, ii, 893).

The results reported by the opening speakers show that respiratory acidosis occurs during anæsthesia as carried out by modern methods, and may have deleterious effects. I would like to recommend caution before going to the other extreme and producing respiratory alkalosis by vigorous controlled respiration.

In this connexion I would like to make three observations:

(1) It is much easier to produce alkalosis by passive overventilation than by active overventilation.

(2) Volume for volume an unbuffered increase in the CO_2 content of the arterial blood produces less change in pH than a decrease. For instance, if we take 50 c.c. and 2·5 c.c. as the combined and free CO_2 content per 100 ml. blood, and the pH as 7·4, an increase of 1 c.c. free CO_2 per 100 ml. lowers the pH by 0·15 unit, whereas an equal decrease in the free CO_2 content causes a rise of 0·2.

(3) Overventilation has been shown to have profound physiological effects, including: tetany; decreased cerebral blood flow (Kety, S. S., and Schmidt, C. F., 1946, *J. clin. Invest.*, **25,** 107); and loss of vasomotor tone (Dale, H. H., and Evans, C. L., 1922, *J. Physiol.*, **56,** 125; Seevers, M. H., Stormont, R., Hathaway, H. R. and Waters, R. M., 1939, *J. Amer. med. Ass.*, **113,** 2131). The latter workers do not attach much importance to their findings, but the rise in pH they deliberately produced is less than that recorded by Dundee in routine practice.

It is obviously difficult, even with exact measurements, to assess the importance of a single variable such as the pH or pCO_2 during the complex situation caused by anæsthesia and surgery. In view of this, and our present limited knowledge of the effects of such gross changes as have been reported, it is obviously desirable that procedures which cause them should be used with caution.

Dr. Cyril F. Scurr said that he was disturbed by Dr. Lucas's concluding remarks, which implied that certain cases had a high CO_2 level despite artificial ventilation. He had always thought that the elimination of CO_2 depended simply on a washing-out process, and that provided the tidal air was adequate and the dead space within reasonable limits carbon dioxide elimination should be satisfactory.

Concerning the possible ill-effects of raised carbon dioxide tension, it was well known that cardiac arrhythmias could thus be caused, and he had often seen arrhythmias disappear following the institution of effective ventilation.

A recent case might suggest another possible adverse effect of carbon dioxide accumulation. In this patient, a child, prolonged paralysis was encountered following the administration of decamethonium iodide. Respiratory depression had persisted for three hours, during which time oxygen was administered continuously. At the end of this time carbon dioxide retention was suspected, and he undertook for five minutes energetic ventilation of the child through a soda-lime absorber. The absorber promptly became very hot, presumably indicating the elimination of considerable CO_2. At the end of this ventilation the respiration of the child immediately returned to normal. It seemed possible that the carbon dioxide led to a condition simulating the curarized state.

Search through literature fails to reveal any work on the effects of CO_2 at the myoneural junction, but it would be very surprising if these high CO_2 levels were entirely without effect there.

Dr. E. K. Brownrigg: Estimation of the alveolar carbon dioxide tension in patients anæsthetized by the Bullough technique would be an interesting study in view of the quiet breathing and reduction of capillary oozing. Would this be a practicable extension of the investigations which have been described?

Hiccup is unquestionably a complex phenomenon. In the conscious patient this distressing symptom can sometimes be treated successfully by inhalations of 5% carbon dioxide.

Hiccup can apparently occur in the fully curarized patient under anæsthesia: this suggests an action of the diaphragm independent of the phrenic nerves.

Dr. Harbord, in reply to Dr. Brownrigg, said that the same procedure to obtain gases from the depths of the lungs could be adopted in patients under anæsthesia using the Bullough technique. As nitrous oxide is soluble in 10% caustic soda, which is used to absorb carbon dioxide in the Haldane apparatus, a saturated solution of caustic soda, as suggested by Prime, F. J., (1950, *Brit. J. Anæs.*, **22,** 162) would have to be used.

Section of Otology

President—Air Vice-Marshal E. D. D. Dickson, C.B., C.B.E., M.D., F.R.C.S.Ed., D.L.O., Q.H.S.

[*December* 5, 1952]

DISCUSSION ON THE MANAGEMENT OF CHRONIC OTITIS MEDIA

Mr. F. McGuckin:

I would begin by mentioning three misconceptions. The first is the notion that chronic otitis media requires neither definition nor description; the second is the idea that the disease is always a sequel to manifest and neglected acute infection, and that therefore it has nowadays disappeared; the third is the naïve belief that the chronic-ear surgeon is a rather squalid relation of the patrician fenestrator.

Taking these points in reverse order, I suggest at the outset that when a surgeon has attained a skilled fenestration technique, he has acquired part of one of the many skills necessary to the proper management of chronic otorrhœa. Next, I believe that we now see an increasing proportion of cases in which the disease is already chronic when the patient first has a symptom of any kind, though I do admit that in the past a considerable mass of chronic disease did arise from manifest and usually destructive acute lesions. In short it is my belief that the process is often of insidious development, so that recognition is important and it may be difficult. Lastly, we are in danger of talking at cross purposes unless we agree on premises; for want of succinct definition I must employ description.

It may be useful to group chronic lesions and their sequelæ in the following fashion:

(1) *Post-inflammatory conditions*, showing the inactive residue of past activity. This group does not concern us in this discussion.

(2) *Recurrent otitis media*, comprising those cases presenting suppurative exacerbations spaced by periods of quiescence or inactivity. I do not regard this as true chronic otitis media, but it must be considered, since skilled management of a particular exacerbation may terminate a potentially prolonged activity.

(3) *Continuous chronic otitis media*, a blunderbuss term in which I take no pride. Nevertheless it implies a process of two, or ten, or forty years' continuity, something showing no easy tendency to spontaneous arrest; and hence it is a condition sharply defined from the second or recurrent group which shows a repeated leaning towards spontaneous improvement.

I shall limit myself to groups 2 and 3.

The patient must first be assessed as a whole. He must say why he comes, and why he comes *now* at this precise moment in five or fifteen years of otorrhœa. Is his cardinal complaint *deafness*, *discharge*, or *discomfort*—and if it is discomfort, is it mental unease, or physical unease, or both? Suppose the cardinal complaint to be *discharge*, its quantity and its smell, then it is necessary to decide the chance of relief; if it is *deafness*, we must say that it may or may not be relieved, and not by default leave the patient with the idea that hearing will return; if *discomfort* is the presenting symptom we must assess whether a comforting word, or minor therapy, or extensive surgery, is necessary to future well-being. I believe that the patient must be disappointed unless at the earliest moment he is told what is the optimum possible result we hope to produce and what is likely to be the most economical method of attaining it. He should understand that the result may be a restored ear, or a dry perforation, or perhaps a radical mastoid cavity, clean or dirty. Assuming that the need for surgery is obvious, the patient should know whether the primary aim of operation is safety, or a dry ear, or restoration of function.

I have tried to construct a scheme which may be helpful in clinical practice (*see* Table I).

Let us consider two extreme cases. The history of the first suggests a possible intracranial invasion and examination adds to the suspicion. The course is clear and the patient is at once advised to come into hospital. In the second case, there is a little difficulty, but, being encouraged to talk, it presently emerges that a friend was recently taken to hospital with a brain abscess said to arise from a running ear. Our patient's running ear has suddenly acquired importance, at least to him. The assessment makes it obvious that once or twice a year there is a brief discharge from an exposed promontory. This patient needs only the management of comforting words, and he may well be better off with no treatment now or at any other time.

At first sight I try to picture the kind, extent and accessibility of the lesion in order to place the case into one of three provisional categories.

(1) *The accessible group*—for example the large perforation with activity in the mucosa of the exposed inner wall, or the small sticky crust which eventually is proved to cover a lesion limited to the external mucosal sac of Prussak's space.

TABLE I.

PRIMARY CLINICAL APPROACH = WHY DOES PATIENT COME AND WHY NOW?

CARDINAL COMPLAINT

DISCHARGE		DISCOMFORT/DANGER
Personal Nuisance e.g. Need for Wool Plug	Social Nuisance e.g. Fœtid Odour	N.B. Chronic Otitis Media is a Potentially Erosive Disease

Local Involvement*	Intracranial Involvement†
(1) Of hearing mechanism	(1) Lateral sinus thrombosis
(2) Of facial canal	(2) Leptomeningitis
(3) Of labyrinth	(3) Brain abscess

*Patient probably not "ill" †Patient probably "ill"

N.B. in chronic otitis an "ill" patient = intracranial complication until proved otherwise.

DEAFNESS

PATHOLOGY: (*a*) Destructive, e.g. Enclosed Ossicular Erosion
(*b*) Fixative, e.g. Fibrosis, Masses of Cholesteatoma, Gross Granulations, &c.

Unilateral	Bilateral
Inconvenient but not socially crippling; often noted accidentally	May be socially crippling May be so insidious as to be first noted by others

OTOGENIC INTRACRANIAL DISEASE

Points for Consideration

(1) The patient is ill or suspect
(2) Local pain or discomfort
(3) Headache
(4) Vomiting
(5) Drowsiness
(6) Pulse-rate
(7) Temperature
(8) Less important things such as stiff-neck, rigors, cells in C.S.F., papillœdema, &c., where diagnosis is clear

(2) *The inaccessible group*—for example the crescent of cholesteatoma extending from the anterior attic over the ossicles into the antrum and perhaps beyond; or the granulating chronic osteitic lesion with an erosion extending possibly to the dura.

(3) *The uncertain group*—partaking of the hopes of the accessible group (1), and the fears of the inaccessible group (2), and about which we can be reasonably sure of only one thing, namely that there is no urgent need to make a decision now, here, at this moment. A case may be transferred to group (1) next week or next year, or it may go into group (2) to-morrow or in 1955. Experience and time will control the speed of such a decision, and I stress that both experience and time are necessary in this category.

Now considering groups (1) and (2), and eventually all cases will fall into one or the other, the principle in treatment should be clear enough. The accessible cases are treated by minor interference, perhaps medical or minimally surgical; the inaccessible cases are submitted to a procedure which to some extent converts the inaccessible into the accessible—though I will show that it also does other things. This means surgery in some form, but as yet it does not commit me to drainage or excision, to conservatism or radicalism.

Active chronic otitis media implies a balance of forces which for the time being is weighted in favour of the offensive. How to alter the balance in favour of the defensive is the business first of nature and then of therapy. Intelligent therapy demands study of all the factors concerned. Let us look at some of the forces.

Bacterial, and sometimes fungoid, invasion is obvious on the one hand, as is poverty of blood supply on the other, but the relative importance of these things is difficult to estimate. The mere fact of poverty of blood supply should suggest a local nutritional defect in soft tissues and in adjacent bone. Perhaps we give too little attention to this kind of change, something influencing both attack and defence, something which may be immensely more important than any infective agent, something which should cause us to reflect on the similarity between our problems and those of the unhealed burn, the varicose ulcer, the long bone osteitis, or the obstinate thoracic empyema. Consider, too, how little infection has to do with those erosions which accompany clean cholesteatoma, and also

that there must be something other than pressure to explain the loss of bone in these cases. Observation of a sufficient number of cases makes it plain that a clean cholesteatoma matrix is not necessarily found in a smooth cavity. It may be found embedded in a pitted necrosis of bone, in the malleus head, the incudal body, the floor of the aditus, and so on. A satisfactory looking matrix may hide a gelatinous kind of granulation tissue which itself covers an osseous erosion of the labyrinthine wall. Granulations may be covered by sheets of keratinizing epithelium, not to be distinguished structurally from cholesteatoma, and these sheets may here and there dip down into the pits left by minute sequestration of bone, a process arising from a shallow chronic osteitis. These observations bring up the question of drainage, which I hold to be of small value in chronic otitis. There are numerous cases in which disease has been arrested spontaneously, but is it clear that this is all due to drainage, or even mainly due to drainage? A careful study of the post-inflammatory, or post-cholesteatoma, scars and erosions should at least raise a suspicion that separation and casting off may be as important as drainage, possibly more so. Good well-drained uniform radical cavities can be dirty enough and they are not rare.

In long standing disease, therefore, my surgical attack tends to be excisive, not a drainage operation, and it includes the most careful removal of every scrap of cholesteatoma matrix, under microscopy if need be—save only when common sense tells me that function will be damaged merely to keep a rule. This really means that I employ the somewhat nebulous support of drainage only when the alternative promises to be more damaging.

I hope I have shown that, *even if the whole of the pathological area is accessible*, we must not expect to solve every problem by easy resort to the antibiotics. It is true that these have certain values, but they also have some dangers, of which the greatest is carelessness, and, after that, drug-fastness, the encouragement of fungi, and skin sensitivities.

To summarize I would present three points: (1) Topical anti-infective therapy must fail if disease is not locally accessible. (2) Systemic anti-infective therapy must fail if blood supply is inadequate. (3) Both must fail if infection is unimportant, as it often is—e.g. irreversible pathology, nutritional defect, cholesteatoma, &c.

Some accessible lesions are of such a nature that minor measures will not serve, and occasionally an inaccessible lesion proves not to possess an irreversible pathology. Yet I find the grouping useful in clinical practice.

In the first group I may employ simple mopping, or some antibiotic or chemical treatment; perhaps I may resort to suction clearance of a single seed of attic cholesteatoma, or remove a sticky crust over Prussak's space; occasionally the removal of a deep granulation or an adital segment polyp proves all that is required; and often the best treatment is to stop treatment.

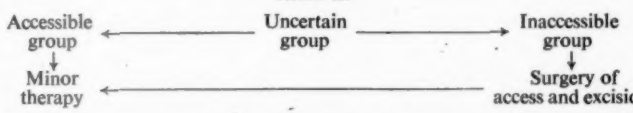
In the doubtful group, observation and therapy combined will at some stage enable me to change the category.

In the inaccessible group surgery should be employed, either conservative or radical. This demands the exact definition of every structure in the middle ear. I take the view that where the soft tissue lining of the cleft has been the site of continuous disease for ten, or twenty, or fifty years, the pathological changes are irreversible and excision is the only principle worth considering. Likewise chronic osteitis with its minute multiple sequestration is subject to the same consideration, always provided that in both cases enthusiasm is tempered by some respect for certain necessary structures which pass through the cleft.

In short, in long-standing lesions I employ the principles of accessibility and excision, not the principle of drainage. And this has nothing to do with function. It is possible to be radically excisive with some areas of the cleft, and yet to be functionally conservative with other parts. Moreover, functional conservation is impossible, though some *anatomical* conservation may be possible, if disease has already disrupted the middle-ear mechanism.

That I consider operation to be no more than a stage in treatment may be illustrated by Table II.

TABLE II.



Brief review of twenty three years' work.—At the outset a steady stream of intracranial complications provided a fascinating field for study and over the years the results were quite good. Between 1929 and 1935 I saw 39 brain abscesses; between 1935 and 1946, 225 cases of major intracranial disease came into the department and of these 86 were proved lateral sinus thromboses. In 1948 I started the system of entering every major operative case on sheets placed on the walls of my dressing room, and six examples from different periods are shown in Table III.

All the cases are there, about 400 of them in one hospital, and I see personally about 90% of all attendances. The material is taken as it comes, nothing is rejected. If in my view operation seems desirable it is carefully discussed with the patient, or the relatives, and usually time is given for reflection on the pros and cons. It matters not whether the discharge has been present for fifty-five

years, or whether this is the eighth operation. Some complain only of discharge, or of deafness; some come in with intracranial lesions, others with facial paralysis. With a fairly strict standard the incidence of unnecessary operations may be 1 or 2%. Satisfactory local results have risen from about 20% in 1947 to not less than 80% to-day, though the incidence of really bad cavities is not much more than 5%. A warning, however, is necessary. Of every 100 cases becoming epithelialized in say three and six months, 20 or 30 will break down again within a year and present new, if more easily solved problems.

TABLE III.

Name Age	Cardinal complaints	Duration of suppurative otitis media	Type of operation	Progress
H. L. 28	Otorrhœa Fœtor	Continuous 23 years	Right endaural transattic radical. 18.11.48	⟶
F. G. 38	Vertigo+++ Failed operation	Continuous 28 years	Right endaural radical +labyrinthectomy 6.4.50	
R. P. 23	Facial paralysis Rigors	Intermittent 20 years	Right endaural transmastoid radical 20.12.50	
S. P. 15	Post-aural swelling	Continuous 7 years	Right combined radical +post-aural "bridge" repair 8.2.51	
P. M. 11	Otorrhœa Fœtor	Continuous 9 years	Left endaural transadital attico-antrostomy. 14.7.51	
J. B. 25	Bilateral otorrhœa	Continuous 18 years	Left endaural transantral attico-antrostomy. 6.2.52	

This paper contains no bibliography, but it does derive both from my predecessors and my contemporaries; from Whillis, McKenzie, Fraser and Tweedie; from Lempert and Thorburn and others too numerous to mention; and not least from Tumarkin, though the acknowledgment may surprise him.

Mr. Gavin Livingstone: In the management of chronic otitis media some opinions support early operation and others prolonged conservative therapy. I would like first to discuss non-operative treatment, but would point out that at operation I have almost invariably been surprised at the degree of disease present, and in many cases I am quite sure I have wasted two or three months in attempting to dry up the ear by dry cleaning.

The conservative treatment of chronic otitis media is influenced, and must often be modified, by social and economic factors. The disease by and large is of the lesser educated classes, and the percentage of cases varies with different types of residential areas, being much higher in the industrial and mining districts.

At Oxford the area feeding the hospital is partly rural and partly industrial, and has a population of roughly 275,000. During the last two years the total attendance of new cases of ear discharge was 437: I operated on 98 cases, and my colleague Mr. R. G. Macbeth on about the same. This means that out of this population, about 100 cases a year need operations.

We find that wage earners are not prepared to miss work on account of what they think is a minor complaint, and only report when their deafness increases, or complications arise.

The careful cleansing of the ear is an extremely important part of the management of chronic otitis. Patients should have treatment, daily if possible, otherwise two or three times a week, at the time of day when the workers can attend, either before 9 a.m. or after 6 p.m. at E.N.T. clinics. The same person should deal with the same patient each time. If it is left to a nurse, she should be a permanent or semi-permanent member of the department, and able to use a head mirror properly. A registrar or senior should examine the ears after the cleansing, until he is sure that this is being carried out correctly.

Equipment.—Suction is essential in an E.N.T. clinic because of its speed and efficiency in cleaning ears especially those with mucoid discharge. But in unskilled or semi-skilled hands syringing is still the most efficient means. The syringes must work smoothly and be small enough for a nurse to use in one hand. Whatever wool-carrying probes are used, they must be able to go through the smallest speculums. The Tumarkin twisted wire carriers are excellent. I prefer, however, the ringed-end Jobson Horne probe. Orange sticks are too big and clumsy, and usually push debris farther into the ear, and bruise the meatus.

The three main types of affected ears are: (1) The mucoid ear. (2) The ear with granulations and cholesteatoma (mastoid infection). (3) The ear with attic suppuration.

Group 1 is a different type of infection from Groups 2 and 3, both from the functional result and the prognosis as to a dry and healed drum.

Group 1: *The mucoid ear.*—This ear usually has a large perforation, probably anterior, but it may vary. The discharge is mucoid and inoffensive, and dries up frequently but may recur with naso-pharyngeal infection. The hearing is not markedly affected, and often patients say they hear better when the ear is moist. These cases do not present much of a problem, and are what I call safe ears.

In children the post-nasal space must be made healthy. Adenoid tissue, especially around the eustachian tubes, should be removed, but I would like to give a word of warning against repeated attempts at removal of adenoid tissue when nasal obstruction is the main trouble. The sinuses should be checked, and infection suspected if the ear condition persists. Allergy may account for some of these persistent cases, especially if the nasal mucosa shows hyperplastic rhinitis. The main disease is in the mucous membrane, which will recover unless bony changes have occurred.

Local treatment to the ear consists of dry cleansing and suction, and the prevention of secondary infection from without. Bathing or swimming should be specifically forbidden.

In the mucoid ear in adults there is usually a large central or kidney-shaped perforation. Careful dry cleaning is sufficient to clear up the discharge, but septic foci in the nose and mouth should be removed, especially infected teeth. Systemic penicillin often has a dramatic effect if the organisms are susceptible, but the greatest discretion should be exercised in the systemic use of all antibiotics.

With the local use of antibiotics the skin of the meatus may become very easily sensitized, and a nasty otitis externa may develop. Prolonged use of any of the combinations invites trouble. I never use penicillin with sulphathiazole, if there is any squamous epithelium present. Aureomycin 250 mg. to 1 gramme of boracic acid is excellent but tends to cake and is then difficult to remove. Chloramphenicol 5% in sterilized starch powder has the best physical properties, and I am at present using it for insufflation.

For local treatment *Groups* 2 and 3 can be considered together. In the ear with granulations and cholesteatoma the discharge is always persistent and unpleasant, usually of many years' duration, but varying in amount. The hearing is much more affected than in the mucoid ear or the ear with attic suppuration. The mastoid is sclerotic and the antrum enlarged or eroded. With attic suppuration the discharge is often minimal although always offensive, and the hearing at first is not markedly affected, but as cholesteatoma spreads across the ossicles, it will deteriorate rapidly.

Conservative treatment of the chronic discharging ear.—T. M. Banham states that while the perforation remains unhealed, chronic otitis can never be said to be cured (*J. Laryng.*, 1945, **40,** 307).

Mr. Colin Johnston, in his series, concluded that although conservative treatment will result in cessation of infection in a high proportion of cases, the prospects of a life-long cure are poor (*Brit. med. J.*, 1948, ii, 1049).

Lewis advocates the use of chloramphenicol 15% in propylene glycol, and produced a remarkable series of dry ears, but I have not succeeded in getting so high a proportion, although I have used many methods of removing debris, including suction, syringing with an attic cannula, and drops of spirit and acetone in equal parts to loosen the cholesteatoma (Lewis, R. S., Gray, J. D., and Hewlett, A. B., 1952. *J. Laryng.*, **66**, 142).

I have concluded that although the chronic ear belonging to Groups 2 and 3 may dry up, and the tympanic membrane become intact, it is this type of ear which should be viewed with suspicion. It should be followed up very carefully, as there must still be cholesteatosis present which will lead to a steady deterioration in the hearing.

There seems more hope of cleaning up the mastoid type of infection than the attic. This is partly due to the way in which granulations and polypi can be treated. The large single ones can be removed in Out-Patients (after careful cocainization), but by twisting rather than snaring them off. Sometimes after this procedure there is a dramatic cessation of discharge and improvement in hearing. These cases, however, should always be seen the following day, although I think the danger of labyrinthitis nowadays is exaggerated. I do not like frequent use of chemical cauteries. I remember two cases where the sequestra that came away after cauterization proved to be the promontory and lower whorl of the cochlea.

Aseptic aural surgery.—Due to the advances in magnification, antibiotics, and the nearly bloodless field produced by modern anæsthesia, the time has come when the whole field of the surgery of the chronic discharging ear should be reviewed. Whatever the operation undertaken, it should result in a safe ear, and the preservation or improvement of the residual hearing.

Rapid recurrence of granulations suggests activity and is an indication for exploration. Again, if a new case shows cholesteatoma which I am unable to remove after a short period of dry cleaning, or if I suspect that more cholesteatoma exists in places where I cannot see, I feel that the best and safest treatment is to operate and to look inside the middle ear. This especially applies to the attic type of perforation where the hearing is good. There is little to lose and much to gain by looking inside, particularly before the ossicular chain is broken, or before the footplate of the stapes has become bound down in a mass of fibrous or granulation tissue.

The radiologist is becoming more and more help in deciding in which cases the destructive processes

are extending. The mentovertical view especially may show antral enlargement and erosion, and may even show cholesteatoma, although only too frequently cholesteatoma is found when none is shown on the film.

If cholesteatoma is present, whether it is in the attic region or elsewhere, increasing deafness is an indication for operation. There is less risk to the hearing by operating than by waiting. The ears with attic perforations may start with good hearing, but as the ossicular chain becomes involved, it gradually deteriorates. Unfortunately, only too often by the time the case is seen, the hearing is already poor.

In these early cases of attic suppuration, an operation may result in a dry ear if the outer attic wall is removed, and the overhang eliminated. Frequently the cholesteatoma can be teased out from around the ossicles, and no further interference is required. The amount of surgery needed must vary with each case, and no set procedure should be adopted. In deciding what to do, the guiding factor is the disease present, and this must be removed in its entirety.

In all operations for chronic ear disease I prefer the endaural approach, but I use the post-auricular incision in the reopening of an old mastoidectomy, or if there are many cells present. The approach is a matter of individual choice. I try to preserve a complete tympano-meatal tube until I have decided what has to be done. In many instances no further flap need be cut, but in these cases I usually remove a semilune of cartilage from the pinna to allow a larger opening to the external auditory meatus. This operation has come locally to be called a "Daggett" as it conforms to the principle of leaving the meatus intact.

In cases of advanced deafness, or where the incus is found to be necrosed or bound down, it should be removed together with the head of the malleus; the hyperplastic or the cholesteatomatous membrane should be lifted from behind forwards, and rolled off the floor of the antrum and the inner wall of the ear. Magnification, good illumination, and as dry a field as possible are necessary. Sometimes it is found that the stapedius muscle still fixes the head of the stapes, and this allows the membrane to be stripped out of the oval window, with little risk of removing the footplate. The round window is easier to clear. If the windows can be cleared of granulations or cholesteatomatous membrane, the hearing is greatly improved. I do not curette the bony eustachian orifice, but strip the lining around it. The facial ridge should be taken down to its limit, and I like the posterior wall of a radical cavity to be as oblique as possible to allow better inspection.

I like working from the antrum or middle ear backwards into the mastoid, rather than the other way round, removing as little dense bone as possible. I use a polishing burr to smooth the surface and remove any small bony sequestra. In cases where I have had to cut the meatal flap I use a very thin skin graft cut with a Humby knife; I get a consistently thin graft with it, and the thinner the graft the more likely it is to take. Whether the graft takes or not, it makes a very good dressing for the raw bone surfaces. I pack with plastic sponge, and leave for seven days, and after that use no further packing.

Intracranial complications are referred to the neuro-surgical department, and I have noticed, when such a case returns to us to have the mastoid opened, that the rest in bed and the high-powered therapy received there have made the ear strikingly clean, despite the fact that it will have had little local treatment.

SUMMARY

(1) Facilities should be available for cases to have daily treatment.

(2) With recent aids to aural surgery, operation should not be postponed until the hearing has deteriorated.

(3) The type of operation must vary with the pathology. The aim of treatment should be to remove the disease completely, and to provide a safe ear, a hearing ear, and a dry ear.

(4) All cases should be followed up at regular intervals for at least five years or longer after they are healed.

Mr. J. Angell James:

The term chronic otitis media covers any chronic inflammation of the middle ear whether catarrhal, suppurative or cholesteatomatous in type and whether the organism is the tubercle bacillus or the *Treponema pallidum* or one of the non-specific organisms. I shall limit my remarks to chronic suppurative otitis media caused by non-specific organisms.

The word chronic is used simply in its strict sense in relation to time. The arbitrary period of three months' duration is taken to divide acute disease from chronic. Thus by definition all cases of chronic otitis media are sequels of acute otitis media.

In addition to inflammation of the middle ear all cases of chronic suppurative otitis media have a perforation of the tympanic membrane. They can be divided for clinical purposes into three groups: (1) Healed; (2) Quiescent; (3) Active.

Group 1 consists of cases in which the disease has resolved and the perforation has closed.

Group 2 consists of cases in which the inflammation has resolved, but a dry perforation persists. Recurrent attacks of inflammation may occur in this group.

Group 3 consists of the cases in which active infection and inflammation persist. These cases have a patent perforation and constant discharge with perhaps short remissions of dryness.

The management of Group 1 is simple. No treatment is necessary unless the perforation is closed by only a thin sheet of epithelium. In this case a warning should be given of the risk of rupture by sudden pressure changes as in syringing, diving, violent nose blowing or sudden depressurizing.

The management of Group 2 may be discussed under three headings: (*a*) These patients are warned of the risks of injury to the inner ear by exposure to loud noise and the risk of infection of the middle ear from fluids or dust entering the external auditory meatus or from the spread of infection from the skin of the external canal or pinna.

(*b*) If the original cause of the otitis was an ascending tubal infection any primary focus in the nose or nasopharynx should receive attention. The common conditions that require treatment are chronic sinusitis, deviation of the nasal septum, hypertrophy and infection of the adenoids either central or tubal, chronic tonsillitis and more rarely neoplasms of the nasopharynx. Special mention should be made of the importance of adenoids. I know of no operation that is more often incompletely performed than adenoidectomy. Residual or recurrent central or tubal adenoids are often overlooked and present a difficult problem in diagnosis and treatment. The diagnosis may require not only a most careful examination of the nasopharynx with a mirror, but also naso-endoscopy, eustachian catheterization with estimation of inflation pressures, soft tissue X-radiography and digital palpation under anæsthesia.

A skiagram is of great assistance in demonstrating the depth of the central adenoid mass. If the depth of the central adenoids is more than half a centimetre surgical removal should be employed. High voltage therapy or radium may be applied later for the lateral fringes and the tubal adenoids in the orifice of the tube if these do not resolve spontaneously after the main mass has been curetted. Diffuse lymphoid hyperplasia of minimal depth and lymphoid tissue in the eustachian tube may be treated satisfactorily by high voltage therapy.

(*c*) When the middle-ear infection has resolved and the primary cause has been removed an attempt may be made to stimulate the margins of the perforation to proliferate and close it. The perforation should be bridged by a disc of finest Cargile membrane, gutta-percha or cigarette paper smeared with Allantoin 4% ointment or moistened with saline. If the margins are epithelialized they should be cauterized first very lightly with trichloracetic acid. Such a bridge may be left in situ for several weeks provided it is kept under observation. At the same time the hearing is often strikingly improved. I must admit that I have not met with many successes in attempts of this sort, but it is worth employing if the perforation is small. It is obvious that closure of quite large perforations must occur frequently from the number of patients we see who have large perforations of the tympanic membrane closed only with a sheet of epithelium so thin and transparent that it is invisible until it is ballooned out by suction with a Siegle's speculum.

The management of cases in Group 3 differs from the above because there is persistent active infection. Our objectives will be (1) to ensure the patient's safety from dangerous complications, (2) to relieve him from the annoyance and discomfort of discharge and pain, (3) to conserve function, (4) to remove the primary cause of the infection and (5) to restore the tympanic membrane as the natural protection of the middle ear.

Our first duty is to assess the extent of the disease in the middle ear, its effect on hearing and on the patient's general condition and then to decide if complications from spread to the cochlea or vestibular apparatus, the facial nerve or intracranial structures are present, threatened or probable. A decision must then be reached if the persistence of the infection is due to lack of drainage from the middle ear or mastoid, local bone necrosis, cholesteatosis, polypi or to constant reinfection from the exterior through the perforation, or to reinfection via the eustachian tube, or is due solely to the patient's lack of resistance to the particular organism concerned.

A fairly accurate assessment can be made by ordinary clinical methods, but in practically all cases these should be supplemented by careful radiography of the temporal bone and bacteriological examination of the discharge. I do not know of any region in which the interpretation of skiagrams is more difficult, but with long and painstaking practice and correlation of findings at operation much valuable information can be acquired of the presence or absence of bone destruction around the mastoid antrum and attic. For this purpose the MacMillan or Toune projections are particularly valuable.

Having collected all the clinical data, and here I would like to stress the supreme importance of a detailed history, we may now plan the treatment to be adopted.

If complications are present or threatened a surgical exploration of the middle-ear cleft must be undertaken. But if the patient has meningitis or a cerebral abscess this may be deferred while the initial treatment of the complication is being undertaken. As the mastoid process in these cases is almost always acellular or very poorly pneumatized the endaural approach is adopted unless a spread to the posterior fossa is anticipated. A wide exposure of the whole area should be made and a meticulous toilet of all diseased structures should follow, tracing every track until healthy tissue is encountered. The use of magnification with glasses and microscope has improved our operative technique greatly. Not only can we see and excise diseased tissues with much greater precision, but essential healthy structures can be skirted closely with complete safety, and middle-ear components which would previously have been ruthlessly removed can often be retained with advantages in healing and in ultimate function.

If cholesteatosis is present operative measures are almost always necessary. It is only very rarely that one can be reasonably certain that the process is confined solely to the middle ear and adjacent portion of the attic. In such a case one is justified in attempting transmeatal removal with minor excision of the outer attic wall and subsequent careful toilet and local treatment of the infection. In the vast majority of cases a full exposure of the mastoid antrum and cells should be undertaken. All traces of cholesteatosis must be removed.

If polypi are present in the external meatus they must be removed. In many cases an exploratory operation of the mastoid must be performed at the same time because of threatened complications or associated cholesteatosis. There are a certain number of cases in which polypi are present and yet the hearing is good and there is no evidence either clinical or radiological of any dangerous erosion. In such cases it is justifiable to remove the polypi and treat the middle ear conservatively.

Since the war I have had 61 cases of aural polypi out of 479 cases of all groups. 17 cases have been treated conservatively with success, but 10 cases were failures. Against these successes must be placed one case which I did not see personally and in which a polyp was removed; but two months later the patient developed a cerebral abscess and died.

I have always been under the impression that aural polypi like nasal polypi developed as a result of an allergic reaction associated with infection. In an attempt to confirm this Dr. A. L. Taylor has examined a series of aural polypi for eosinophils but unfortunately for my theory no evidence of eosinophilic infiltration has been found. We propose to pursue the investigation for further evidence.

When complications are not threatening and cholesteatosis and polypi are not present we are justified in adopting conservative measures.

The first step is to deal with any ascending infection from nasal or nasopharyngeal infection or allergy and any source of external infection or allergy as recommended for Group 2. But local treatment may be begun at the same time.

The medicaments from which to choose may be divided into physical agents, which include desiccants, decongestants, hygroscopic agents, proteolytic agents and ionization, and antibiotics, antibacterial and fungicidal agents, sulphonamides and antiseptics. It is common practice to combine one of the physical group with one of the second group. Having graduated in the days of boracic acid and biniodide syringing and the insertion of hydrogen peroxide for cleaning followed by drops of spirit and various aqueous solutions of antiseptics I now usually limit myself in the first instance to the use of the appropriate antibiotic according to the bacteriologist's report on the swab taken from the middle ear. If no report were available I should try first of all with chloramphenicol as our figures show that the majority of organisms are sensitive to this antibiotic (Table I). Now that the incidence of

TABLE I.—SENSITIVITY TO ANTIBIOTICS IN PERCENTAGES

	Staphylococci	*B. coli*	*Diphtheroid bacillus*	*B. proteus*
Penicillin	76	5	80	21
Chloramphenicol	84	60	75	73
Aureomycin	90	20	60	25
Streptomycin	70	95	70	94

drug resistance is increasing it is no longer possible to choose the antibiotic or antiseptic according to the variety of organisms alone and the bacteriologist should test the sensitivity of the organism to penicillin, chloramphenicol, Aureomycin, streptomycin and Terramycin, and from the result of the test the appropriate antibiotic is selected.

It is of considerable interest to note the frequency with which different organisms are found in cases of chronic suppurative otitis (Table II).

TABLE II.—INCIDENCE PER CENT

Staphylococci	36%
B. coli	23%
Diphtheroid bacillus	20%
B. proteus	14%
Streptococci	3%
Friedländer's bacillus	1%
H. influenzæ, *B. pyocaneus*, Pneumococci, Anaerobes — combined total	3%

Having made the choice of antibiotic we have still to decide whether to use it in powder form or solution. I think that the powder form is usually the first choice because the drugs are more stable the drying discourages bacterial activity and the concentration of available drug is greater. In a nervous patient any residual powder may be left in the ear for several weeks and finally removed by gentle syringing, provided that meticulous care is taken to dry the cavity perfectly and then to insufflate an almost imperceptible dusting of powder. Solutions make the best vehicle when the discharge is very copious or the perforation very small or the meatus stenosed. The insertion of a dry wick of ½ in. ribbon gauze which is subsequently soaked with a solution of the antibiotic is the most effective method of application, but requires attention once or twice a day and an expert operator. The presence

of the wick helps to dilate the meatus as well as to act as a drain for the discharge and also leaves the meatus clean and ready for the subsequent treatment reducing the time spent in the daily toilet of the ear. When using powder there is always the risk of caking. For this reason soluble vehicles such as powdered lactose or urea are the most suitable diluents as the powder can be removed readily by syringing.

When using drops or powder it is important to stress the importance of a meticulous toilet of the middle ear before applying the treatment and any powder or solution must be applied vigorously and the meatus should be filled completely. Fluids should be allowed to remain in contact for a minute before the excess is allowed to escape. Two or more antibiotics may be mixed and in fact it is probable that the effect of each would be enhanced by this means. Penicillin, however, is decomposed by acids and alkalines and Aureomycin would not be compatible with it.

By means such as these it is usually possible to sterilize the middle-ear cleft, but in an appreciable number of cases drug sensitivity develops to the antibiotic and an acute skin sensitization prevents its further use and it must be replaced by innocuous and sedative applications.

If, in spite of all our conservative treatment, discharge and active inflammation persist the advisability of an exploratory and excisive operation has to be considered. We are faced with the question whether or not to press the patient to have an exploration performed or to explain that he must put up with some discharge and be prepared to keep the ear clean by daily mopping. When the best that surgery could offer was a 25% chance that the discharge would continue in spite of any operation this was a reasonable attitude to adopt, but now that one should achieve a dry ear in 90% with a negligible risk in the process there is little justification for condemning the patient to a life of permanent annoyance and above all to the further gradual deterioration of the hearing and accompanying tinnitus.

SUMMARY

Two advances which have altered our attitude to the management of these cases are the introduction of local treatment by selective antibiotics and antiseptics and the improvement in the results of operation both in hearing and the percentage of dry ears as a result of the application to these cases of the meticulous technique developed for the fenestration operation.

We should no longer be content with an attitude of *laissez faire* even in the so-called safe running ear, but with constant care aided by repeated bacteriological control we should eliminate all the infecting organisms and then if disease persists proceed to excision of the affected tissues retaining with extreme care all healthy tissues that are useful either for their part in aiding healing or in preservation of hearing.

The President said that the three papers had been interesting and stimulating. He endorsed Mr. Livingstone's remark that any form of treatment should be carried out by somebody experienced using proper illumination and instrumentation. To delegate such treatment to patients themselves was an appalling waste of time. In the R.A.F. they were fortunate enough to control the movements of the patients. They had reviewed 200 patients who had received conservative treatment; of these, 82% had dry ears, which had remained dry for from four months to one year; in 9% the condition was unchanged, hearing was improved by treatment in about 40%. The R.A.F., however, was particularly favoured because cases which had had chronic suppuration for years had been as far as possible excluded from entry. As much screening as possible took place before people joined up. Probably the R.A.F. results were influenced by that fact and by their good fortune in getting their cases early. Cases which responded unfavourably were those which had cholesteatoma.

Mr. I. A. Tumarkin said that he desired to refer to the evolution of the surgery of the mastoid. In 1928, Lempert first described a mobile window which could be retracted to provide access to the mastoid cortex. This was essentially a transmastoid operation. Soon afterwards he began to veer towards a transmeatal approach. In 1935 he described a landmark for entering the antrum—at a point two-thirds of the way within the external auditory canal. Ten years later he described a new technique which was entirely transmeatal—the essential feature being that bone removal commenced at the tympanic annulus. This primary attack on the annulus was also utilized by Popper and by Cornelli and was, of course, the characteristic feature of the speaker's operation of atticotomy. When he (the speaker) first thought of this type of operation which, of course, was not new, he was thinking in terms of limited atticotomy. He still thought that occasionally there was scope for a simple opening of the attic but in most cases he found himself compelled to venture more widely into the mastoid process. It seemed that there had been a coalescence of ideas, out of which there was emerging the conception of a flexible technique: an operation which started with the utmost conservatism, which could be stopped at any point, which went immediately to the root of the disease in the attic, and yet could be extended anywhere within the petromastoid complex. Cornelli used a post-aural incision, Popper a pre-aural incision. Lempert excised a large area of endaural skin which he attempted to use as a free graft. The speaker discussed the advantages of his own pedicled flap, which provided ample access and rapid healing.

Mr. Tumarkin then dealt with the pathogenesis of chronic otitis media and its remarkable association with the poorly pneumatized mastoid. Wittmaack deserved credit for the idea that the poorly pneumatized mastoid was one which had never developed but he located the pathological process in some sort

of inflammation which occurred during birth or soon afterwards: some infection of the mucous membrane of the developing tympanic cleft which determined the future structure of the mastoid. The speaker believed, on the contrary, that frustration of pneumatization might occur at any time during the first fifteen years of life. Pneumatization, being concerned with the production of an air system at normal pressure, must be frustrated if for some reason air could not enter or circulate within the developing tympanic cleft.

What was it that could block the eustachian tube? Surely the answer was obvious. The vast majority of slum children suffered with nasal catarrh, for which the misused tonsil and adenoid nomenclature was employed. It was not simple tonsil or adenoid disease but a disease of the whole upper respiratory tract; and blockage of the eustachian tube must occur very frequently as evidenced by the fact that so many of these children showed a retracted tympanic membrane. But it was not realized how widely spread this comparatively latent disease of the middle-ear cleft was. Last year he examined 100 children from one of the poorest schools in Bootle: 73% of the drums were abnormal, 1·5% had frank otorrhœa, and a further 5% had dry perforations.

That was the fundamental problem in otology. They had to tackle not only that 1·5% and the 5% but the 66·5% as well, because that was the reservoir which gave rise to the progressive catarrhal deafness of adult life. It was a herculean problem, for which they would need the assistance of public health authorities, bacteriologists, and so on.

Unfortunately within recent years a totally new theory had been promulgated which, if it were accepted, would paralyse all efforts to deal with this problem. He referred to the work of Diamant and Dahlberg dealing with the mechanism of pneumatization; these authors maintained that acellular mastoids were not abnormal, they were simply normal variants. They said that the size of the cell system was genetically determined, that if the parents had small systems the children would have the same. They completely denied that environmental factors such as eustachian block could have any effect such as he had mentioned. Curiously enough they believed that environmental factors might act *in utero* and in some way influence the ultimate pattern of the mastoid. Lastly, they believed that the small-cell system, although perfectly normal, was nevertheless prone to chronic otitis media, whereas the large-cell system was relatively immune.

According to this theory, the pneumatic pattern of the adult was already stamped on the new-born child. Furthermore, the individual's chance of developing otitis media, being inversely proportional to the size of his mastoid system, was also more or less fixed at birth. It followed that the otologist could not hope ever to influence pneumatization or diminish the incidence of chronic otitis media. This was indeed a sterile paralysing hypothesis and yet the work on which it was based had been carried out with the greatest care. The speaker's considered opinion was that the theory was wrong.

Mr. R. Scott Stevenson said that it was important to emphasize the real value of the fenestration operation, which was that of teaching young otologists the anatomy of the temporal bone. Before the 1914–18 war he thought that too many radical mastoid operations were done, yet many out-patients kept coming up year after year with persistent ear discharge. Between the wars he thought they were inclined perhaps to over-emphasize a conservative attitude. What he learned in the last war in the Services was the value of doing the job of attending to a discharging ear oneself from beginning to end, but that was impossible in civil life, with patients often coming many miles to hospital. He wondered sometimes now, however, whether they were again placing the emphasis too much on operation.

Mr. R. R. Simpson said that it was many years since Ritchie Rodger first maintained that school clinics run by local authorities were the greatest preventive measure in chronic otitis media he had ever known. One of the sad things about the National Health Service was the way in which the Service had interfered with these school clinics in the industrial population. The only chronic otorrhœas they saw now were cholesteatomas in the school population and he saw no prospect there but surgery.

He said how much he appreciated Mr. McGuckin's statement that there must be something other than pressure to explain the loss of bone in the erosions which accompanied clean cholesteatoma. He wished that emphasis on pressure could be put out of the textbooks altogether. He congratulated Mr. McGuckin also on his emphasis on illumination and magnification in doing his radical mastoid operations.

Mr. Terence Cawthorne said that he had been brought up by Arthur Cheatle to believe that chronic otitis media was the result and not the cause of an acellular mastoid, and this view was much more acceptable now than when first propounded. Some twenty years ago when he was working in four Special Ear Clinics of the L.C.C. School Medical Service the amount and variety of chronic suppurative otitis media seen at these clinics was amazing. Dr. A. G. Wells, who had charge of the Special Ear Clinic Service, had shown that between 60 and 70% of these cases cleared up with regular treatment. Banham, for the Royal Air Force, and Johnston, working on behalf of the Medical Research Council in the Factory Otological Scheme, had achieved similar results. Nevertheless, there was a certain proportion that could only be cleared up by adequate surgery and certainly, so far as adults were concerned, he felt that the classical radical mastoid proceeding along the lines of the fenestration operation, without, of course, the fenestra, was the best operation.

Section of Experimental Medicine and Therapeutics

President—Professor R. V. CHRISTIE, M.Sc.McGill, D.Sc.Lond., M.D., F.R.C.P.

[*March* 17, 1953]

Dyspnœa in Relation to the Visco-Elastic Properties of the Lung[1]

PRESIDENT'S ADDRESS

By Professor R. V. CHRISTIE
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RESPIRATION is one of many rhythmic processes but it is almost unique in that its rhythm can at any time be altered by voluntary control. In many respects the only other rhythmic process which is comparable is walking. There is a natural rate of walking at which we are not conscious of any effort and it has been shown that this is the rate at which we are in fact using our muscles most efficiently. A healthy person can increase his pace slightly without conscious effort but if the muscles concerned have to do more than a certain amount of work he immediately becomes aware of effort.

In breathing, just as in walking, ordinary ventilation of the lungs is effortless and a healthy individual can increase ventilation by 100% or more without being aware of effort, but if a greater increase is demanded by the respiratory centres he will become conscious of respiratory effort. During the ordinary activities of the day we breathe at a rate of about 15 per minute, with a tidal air of about 600 c.c. and it is very interesting that, just as in walking at an ordinary pace, this rate can be shown to be the most efficient in that it demands the least amount of work.

The work involved in breathing can be estimated by placing an individual in a Drinker respirator and measuring the actual amount of work required to ventilate the lungs. This has been done by Otis, Fenn and Rahn (1950) who showed that a resting individual does about 0·4 kg. metres of respiratory work per minute, of which about 60% is expended in overcoming the elastic resistance of the lungs and about 40% in overcoming viscous and other non-elastic resistances. It is important to understand just what is meant by these terms and they can best be illustrated by considering the lungs as a pair of bellows, the handles of which are joined by a spring to represent the elastic resistance of the lungs. When the bellows are expanded as on inspiration the spring is stretched, and when the handles are released as on expiration the recoil of the spring is sufficient to expel the air. Three types of resistance are involved in ventilating this system. The first is the elastic resistance of the spring. The second is the resistance of the fabric of the bellows, and this corresponds to the viscous resistance of the tissues which is non-elastic. Lastly, air has to be sucked through the nozzle and this gives rise to both turbulent and viscous resistance of the air which is also non-elastic.

For the sake of simplicity these resistances can be divided into the elastic resistance and the non-elastic resistance, since the physical laws which govern these two main groups are quite different. The non-elastic resistance is chiefly influenced by the speed with which the bellows expand. If the spring were removed it would be most efficient to work the bellows slowly and to full capacity, and in the same way if the resistance to breathing were entirely non-elastic, ventilation of the lungs would be accomplished most efficiently by slow vital capacity breaths. The work involved in overcoming elastic resistance obeys quite different laws. It does not matter how quickly a spring is stretched, whether it is stretched quickly or slowly just the same amount of work is done. What does matter is how far it is stretched, for the amount of work done increases very rapidly with the degree of stretching. For this reason, if only elastic resistance were involved it would pay to work the bellows very rapidly and shallowly, as this would involve the least amount of work. In the same way, if the resistance to breathing were entirely elastic, ventilation of the lungs would be accomplished most efficiently by rapid and shallow breaths at a rate of 40 or 50 a minute.

Otis, Fenn and Rahn (1950) realized the physiological significance of the differences between the behaviour of elastic and non-elastic resistances in the lung, and they therefore applied the established laws of elasticity and viscosity and air turbulence to the measurements they had made on normal subjects in the Drinker respirator. The results they obtained are shown in simplified form in Fig. 1. The individual involved in this experiment is breathing with an alveolar ventilation of 6 litres a minute and it is assumed that the same alveolar ventilation is maintained at different rates and depths of breathing. The respiratory dead space is also assumed to remain constant so that on the right of

[1] The original work in this Communication was done in collaboration with Dr. M. B. McIlroy and Dr. R. Marshall and will be described later in detail.

Fig. 1 where breathing is rapid and shallow the total minute volume respired is greater than on the left where breathing is slow and deep. The lowest curve represents the work done to overcome viscous and turbulent resistance and it is clear that the amount of work involved in overcoming this non-elastic resistance increases quite rapidly as breathing becomes more rapid and shallow. Conversely, the work involved in overcoming elastic resistance of the lungs, which is shown in the middle curve, is greatest when the individual breathes slowly and deeply, and least when he breathes rapidly and shallowly. If the work expended on the elastic and non-elastic resistances is added, the sum will represent the total work done per minute, which is shown by the top curve in Fig. 1 and it is obvious that it must have the shape of a trough because its two components are sloping in opposite directions. If we accept these curves as being valid, the important point emerges that if the lungs are to be ventilated at 6 litres a minute the most economical rate in terms of respiratory work is about 15 a minute which is approximately the rate at which we normally breathe.

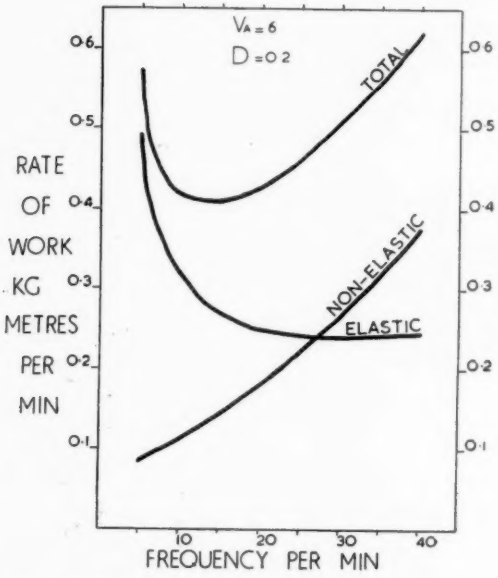

FIG. 1. — Diagram showing the work of ventilating the lungs of a normal subject at different frequencies of respiration calculated from the data of Otis, Fenn and Rahn (1950) at an alveolar ventilation of 6 litres/min. and a dead space of 0·2 litre. The lower curves represent the work expended in overcoming elastic and non-elastic resistance. The uppermost curve represents the total work of ventilating the lungs.

(*Adapted from Otis, Fenn and Rahn*, 1950.)

Before applying this method of approach to disease, I will discuss very briefly the validity of these curves. Otis, Fenn and Rahn measured the elastic and viscous constants of the lung in a number of normal individuals by a complex method which involved passive breathing in a Drinker respirator or plethysmograph. From these constants and from the known laws of elasticity, viscosity and gas turbulence they calculated these curves so that the existence of this trough is largely theoretical.

The technique we ourselves have used is more simple and is based on the fact that the negative intrapleural pressure is a measure of the force exerted on the lung and the tidal air a measure of the amount of distension produced. If these two, the intrapleural pressure and the tidal air, are measured simultaneously the amount of work involved in each breath can be calculated by the method described by Bayliss and Robertson (1939) and confirmed by others. We have measured the intra-œsophageal pressure which is identical with the intrapleural pressure, using the technique described by Dornhorst and Leathart (1952). The tidal air is recorded simultaneously by means of a pneumotachograph and capacitance manometer. From these records the work expended in overcoming the elastic and non-elastic resistances of the lungs can be calculated, the work involved in moving the chest wall and abdominal viscera being excluded. With this technique it is possible to make direct measurements of the work involved in breathing at different rates and depths and thus to confirm directly the calculated curves of Otis, Fenn and Rahn. In Fig. 2 the subject is breathing with a constant alveolar ventilation of 7·6 litres a minute, a respiratory dead space of 200 c.c. being assumed. The respiratory rate was varied from 5 per minute to 40 per minute by following a metronome and the appropriate respiratory depth was obtained by spirometer control. Fig. 2 clearly shows that the respiratory work involved in ventilating the lungs was least when the subject breathed at a rate of about 15 per minute, an observation which confirms by direct measurement the calculations of Otis, Fenn and Rahn depicted in Fig. 1.

With this technique the effects of exercise can also be investigated. This is not possible by the method of Otis, Fenn and Rahn since it would be difficult to exercise in a Drinker respirator and at the same time submit to passive breathing. Fig. 3 shows the effect of moderate exercise, the respiratory work being calculated at various respiratory rates by the method of Otis, Fenn and Rahn (1950). At rest the subject was breathing at 12 per minute and this corresponds closely with the frequency at which least respiratory work was required. On exercise sufficient to increase the alveolar ventilation

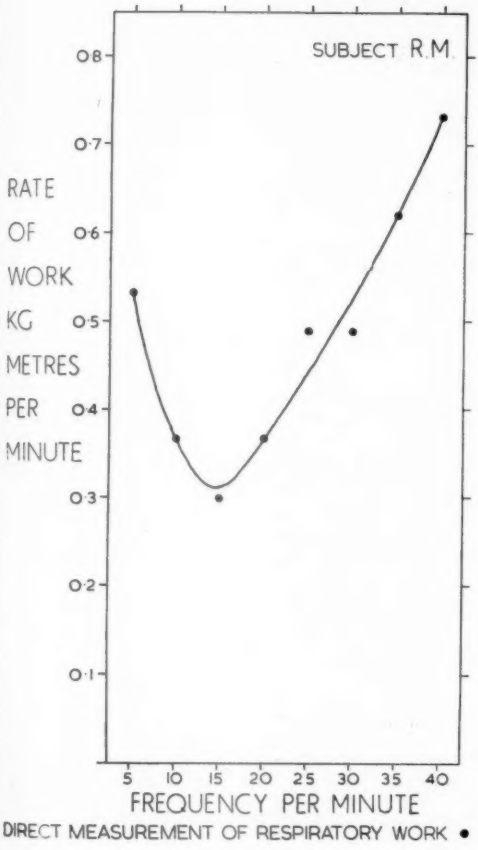

FIG. 2.—Diagram showing the work of ventilating the lungs of a normal subject at different frequencies of respiration. The work involved at each frequency is measured directly.

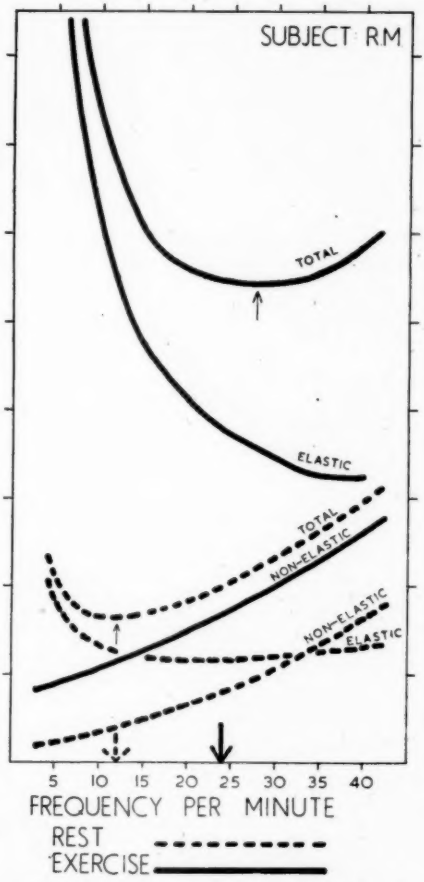

FIG. 3.—Diagram showing the work of ventilating the lungs of a normal subject at rest and during exercise calculated by the method of Otis, Fenn and Rahn (1950). The light arrows on the curves of total work indicate the frequency at which least respiratory work is required. The heavy arrows at the bottom of the diagram indicate the actual frequency of respiration.

from its resting value of 4 litres a minute to 12 litres a minute the respiratory rate rose to 24 per minute, and again this corresponded closely to the frequency at which least respiratory work was required. This observation has been confirmed by direct measurement and it is clear that on exercise as well as at rest the normal individual selects the respiratory rate and depth which is most economical in terms of respiratory work. It is not known how this desirable state of affairs is brought about, but work which is now in progress suggests that it is the Hering-Breuer reflex that is responsible.

The work required to ventilate the lungs of normal individuals and of patients with heart failure is shown in Fig. 4. In heart failure about 1 kg. metre of respiratory work per minute has to be done at rest which is about twice the amount required of the normal control group. On voluntary hyperventilation, sufficient to double the resting minute volume, both normal individuals and patients with heart failure approximately double the amount of respiratory work. But when the same degree of hyperventilation is produced by mild exercise the response of normal individuals and of patients with heart failure is very different. In normal individuals less respiratory work is required to double the ventilation on exercise than at rest and, from this and other observations that we have made, it is clear that in health the lungs become more distensible on exercise. In heart failure the lungs become very much less distensible; on exercise, so mild that the volume of air respired is only doubled, the cardiac patient has to do four or five times the respiratory work of the normal controls and it is therefore not surprising that he becomes conscious of respiratory effort. This may be the explanation of dyspnœa in cardiac failure, but we have to look elsewhere for an explanation of the increase in respiratory rate which is characteristic of this form of dyspnœa.

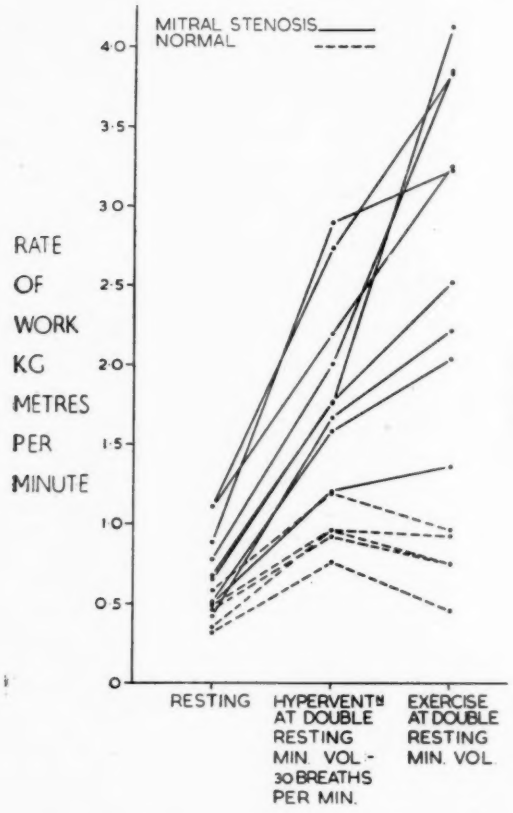

FIG. 4.—Graph showing the rate of respiratory work in kg. metres per minute in normal subjects and patients with mitral stenosis, at rest, on hyperventilation and exercise. In normal subjects the work of breathing is less on exercise than on equivalent hyperventilation. In mitral stenosis the work of breathing is greater on exercise.

Fig. 5 shows the response to exercise of a patient with mitral stenosis and heart failure. At rest the patient was breathing at 21 per minute and this corresponded closely with the frequency at which least respiratory work would be required. On mild exercise, sufficient to increase the minute volume respired to 19 litres per minute from its resting value of 7 per minute, the respiratory rate rose to 29 per minute, and again this corresponded closely with the frequency at which least respiratory work would be required.

Fig. 6 shows the response to change in posture of a patient with heart failure and severe orthopnœa. In the upright position the work of breathing was 0·7 kg. metre per minute and the respiratory rate 19 per minute which corresponded closely with the frequency at which least respiratory work was

FIG. 5.—Diagram showing the work of ventilating the lungs of a patient with mitral stenosis at rest and during exercise. The light arrows on the curves of total work indicate the frequency at which least respiratory work is required. The heavy arrows at the bottom of the diagram indicate the actual frequency of respiration.

FIG. 6.—Diagram showing the work of ventilating the lungs of a patient with mitral stenosis and orthopnœa when sitting up and when lying flat. The light arrows on the curves of total work indicate the frequency at which least respiratory work is required. The heavy arrows at the bottom of the diagram indicate the actual frequency of respiration.

required. On lying flat the lungs became less distensible, presumably owing to pulmonary congestion, and the work of breathing increased to 2·6 kg. metres per minute, a fourfold increase in the work required to ventilate the lungs, and it is not surprising that the patient became acutely conscious of respiratory effort. At the same time the respiratory rate increased to 29 per minute, which again corresponded closely with the frequency at which least respiratory work would be required.

These findings have been confirmed in other individuals with heart failure associated with exertional dyspnœa and orthopnœa. Dyspnœa in these patients, whether due to exertion or posture, is associated with pulmonary congestion which gives rise to a substantial increase in the amount of work required to ventilate the lungs, and it is reasonable to suppose that this is largely, if not wholly, responsible for the consciousness of respiratory effort which occurs. It also appears to be true that in cardiac failure the patient breathes at the rate and depth which is most economical in terms of respiratory work, and that this applies to the rapid and shallow breathing of exertional dyspnœa as well as to the change in respiratory rhythm which occurs in orthopnœa.

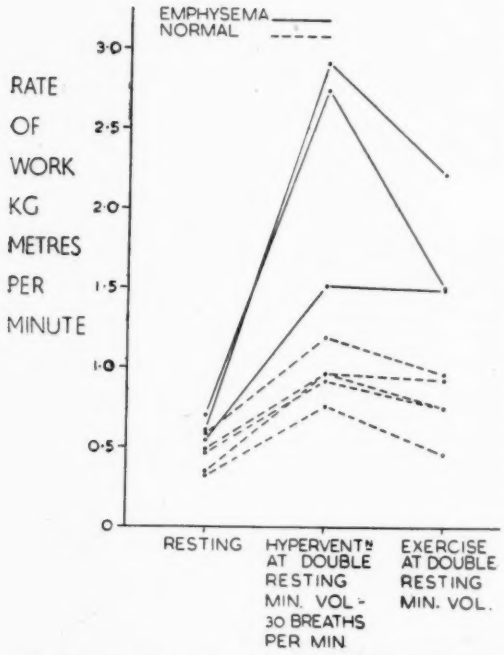

FIG. 7.—Graph showing the rate of respiratory work in kg. metres per minute in normal subjects and patients with emphysema at rest, on hyperventilation and exercise. In emphysema the work required to double the resting minute volume on hyperventilation is greatly increased.

EMPHYSEMA

The work required to ventilate the lungs of normal individuals and of patients with emphysema is shown in Fig. 7. At rest the amount of respiratory work required of the patient with emphysema is within normal limits, but when the minute volume respired is doubled either by voluntary hyperventilation or by mild exercise the amount of respiratory work required may be two or three times that demanded of a healthy individual. This marked increase in respiratory work on hyperventilation is clearly due to a relative increase in non-elastic resistance to expansion of the emphysematous lung: in 15 normal individuals the proportion of respiratory work expended on non-elastic resistance averaged 32% while in 13 patients with emphysema it averaged 66%. Under these circumstances the patient with emphysema must exert an abnormal amount of respiratory effort if he is to increase pulmonary ventilation, and this must be an important factor in the production of dyspnœa and in the limitation of the maximal breathing capacity.

SUMMARY

In normal individuals, whether at rest or on exercise, the rate and depth of breathing is adjusted to the rhythm which is most economical in terms of respiratory work. The regulating mechanism responsible for this adjustment is probably the Hering-Breuer reflex.

In cardiac failure, dyspnœa on exertion and orthopnœa can be explained by the disproportionate increase in respiratory work which is required of the patient, due to pulmonary congestion. The rapid and shallow breathing which is associated with cardiac dyspnœa is shown to be another illustration of the rule that individuals breathe at the rate and depth which is most economical in terms of respiratory work.

In emphysema there is a relative increase in the non-elastic resistance of the lungs to inflation and as a result the respiratory work on hyperventilation is greatly increased. This abnormal increase in respiratory work must at least be an important factor in the production of dyspnœa and in the limitation of the maximal breathing capacity.

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Section of Comparative Medicine

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[*January* 21, 1953]

Ovarian Hormones and Uterine Infection in Cattle

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DURING the last few years we have been investigating the possibility of using moderate or inferior cows as incubators for the development of genetically high-grade germinal material. Preliminary investigations in rabbits proved highly successful with most of the transplanted ova being successfully carried to term, and in this species it has been possible to store fertilized ova at reduced temperatures for several days and then to transplant them successfully. When attempts were made to repeat these findings in the cow they consistently failed despite the fact that many workers all over the world were engaged on the problem. There was, however, a certain difference in technique, for whereas in the rabbit the ovum transfer had been an aseptic surgical operation, in the cow the ova were placed in the uterus by means of a pipette passed through the cervical canal, and complete asepsis was therefore extremely difficult.

It was thought at first that lack of success was due to death of the ova as the cow egg is much more difficult to culture than the rabbit egg, and precautions regarding temperature shock on handling the material were introduced, all without success. It was then decided to carry out a number of transplants using the normal technique of introducing ova via the cervix at four to five days' post-œstrus and to slaughter the cows and examine the uteri clinically and bacteriologically. In almost every case the uteri contained a considerable quantity of pus. In view of the fact that artificial insemination procedure is identical to the technique used in this work, and that it is highly successful when carried out at œstrus, this phenomenon was rather surprising. After discussion with Dr. R. M. Fry of the Public Health Laboratories at Cambridge, who has carried out almost all the bacteriological work in these investigations, it was decided to investigate the matter further.

We are fortunate in having cows for short-term research projects loaned by the Ministry of Food. They are housed in a straw yard with a vasectomized bull to detect animals in œstrus. Cows required at œstrus for these experiments were chosen by the appearance of œstrous behaviour, while those required in the luteal phase were chosen by manual examination of the ovaries *per rectum* for the detection of a full-sized corpus luteum. All selections were confirmed at slaughter by post-mortem examinations of the ovaries.

Our investigations can conveniently be divided into five phases. Our first experiments were designed to compare the effect of artificial insemination during œstrus with insemination during the luteal phase of the cycle. In view of the importance of this work to artificial insemination of cattle, we decided to use bull semen during the early studies. Each semen sample was examined culturally to compare bacteria contained therein with any recovered from infected uteri. After the first results were reviewed certain modifications of technique were found desirable and the reasons for these changes will be discussed later.

In all our experiments every animal was examined prior to treatment to eliminate those with clinical abnormalities of the genital tract and then a cervical swab was taken from the mid-point of the cervix using a sterile sheathed swab and sterile speculum. In most cases, however, the culture of these swabs proved negative. Immediately after taking the swab, the infected material (semen in the first experiment) was introduced into the uterus using an inseminating syringe and pipette, which was guided into the uterus by manual fixation of the cervix *per rectum*.

In the first experiment 6 cows were inseminated at œstrus with infected semen and 11 were inseminated during the luteal phase with similar samples of semen. The animals were slaughtered two days after insemination and the uteri removed for cultural examination. Bacterial swabs were then taken from the mid-point of the right and left uterine horns and from the body of the uterus. Smears from these swabs were cultured at 37° C. aerobically, anaerobically, and in air with 10% CO_2. A summary of the results is given in Table I.

TABLE I.—RESULTS OF UTERINE INFECTION IN CATTLE AT VARIOUS STAGES OF THE ŒSTROUS CYCLE

	No. of cows	No. with pyometra	No. infected on culture of uterine swabs
Infected during œstrus	6	0	0
Infected during the luteal phase	11*	9	9

* In 2 cows the semen used proved to be practically sterile on culture.

The results show that in every case where cows were inseminated during œstrus with semen containing *C. pyogenes*, a pus-producing organism, the uteri were sterile two days later. 9 out of 11 cows inseminated during the luteal phase had pyometritis. In 1 animal it was a sterile pyometritis, while in the remaining 2 no pyometritis was present, probably due to the fact that the semen used for these animals contained a few saprophytes only.

While the majority of bovine semen samples contain appreciable numbers of bacteria it was decided in future work to add to any sterile semen samples a standard culture of *C. pyogenes* which had been isolated from bull semen by Dr. R. M. Fry. This culture was prepared in advance and freeze-dried in small doses for subsequent experiments.

While our first experiment showed that resistance to infection varied during the œstrous cycle it was necessary to determine whether or not the ovarian hormones were responsible for this change. For this work ovariectomized cows were required and so 9 cows were ovariectomized *per vaginam* and left for at least fourteen days for endogenous ovarian hormones to be eliminated from the body.

4 of the 9 animals were inseminated with infected semen after taking cervical swabs. 2 cows were injected intramuscularly with 25 mg. stilbœstrol, and cervical swabs taken the following day when they showed signs of œstrus. Infected semen was then inseminated into the uterus and no further hormone treatment was given. The remaining 3 cows were given 25 mg. stilbœstrol, followed by daily intramuscular injections of 50 mg. progesterone in oil. After four days of progesterone treatment, they were inseminated with infected semen, and the daily progesterone injections maintained until slaughter. All cows were slaughtered two days after insemination and the uteri removed, as before, for bacteriological examination.

A summary of the results is given in Table II. Of the 4 ovariectomized control cows, 2 had a sterile pyometritis. A further animal had a pyometritis which was sterile in aerobic and CO_2 cultures, but a few colonies grew in the anaerobic smears. The remaining animal had no symptoms of pyometritis and the uterine swabs were sterile. It is perhaps significant that at slaughter this latter animal had two 8 mm. follicles present on some ectopic ovarian tissue. The 2 animals receiving stilbœstrol had sterile uteri which appeared normal and healthy while those receiving progesterone all had a gross infected pyometritis.

In the ovariectomized control cows the bacteria introduced with the semen were absent two days after infection. Thus it appears that in the intact animal it is progesterone which promotes conditions in the uterus favourable for bacterial development, for under the influence of exogenous progesterone in ovariectomized cows an infected pyometritis developed (Table II). This effect may be allied to

TABLE II.—RESULTS OF UTERINE INFECTION IN OVARIECTOMIZED COWS

Hormone treatment	No. of cows	No. with pyometra	No. infected on culture of uterine swabs
None (control)	4	3	0 (1)*
+ stilbœstrol	2	0	0
+ stilbœstrol + progesterone	3	3	3

*See text above.

the fundamental role of progesterone in promoting conditions in the uterus suitable for the developing zygote. Alternatively exogenous œstrogen helped to prevent bacterial development and prevented the accumulation of pus. This effect may explain why cows conceive more readily if allowed two to three months before post-partum service, by which time the heat periods would ensure that any infection introduced at parturition is eliminated.

We had thus established that ovarian hormones could affect the resistance of the bovine uterus to infection. We were interested to determine the effect of antibiotics on this development of pyometritis. Did the level of antibiotics added to semen in routine artificial insemination practice prevent pyometritis when cows were inseminated during the luteal phase? Experiment 3 was designed to investigate these problems. A sample of mixed semen was split into two portions and a culture of *C. pyogenes* was added to one half. To both samples of semen antibiotics and sulphanilamide were added to give a final concentration of 1,000 i.u. penicillin per ml., 500 i.u. streptomycin per ml., and 0·3% sulphanilamide. The semen samples were then stored for twenty-four hours at + 5° C. We had employed this level of penicillin and streptomycin in the blood serum used as a flushing medium in our unsuccessful efforts to transplant bovine ova from which attempts pyometritis had resulted.

After the standard preliminaries of taking cervical swabs, 3 cows were inseminated with each batch of semen, and all cows were slaughtered two days after insemination. The results, presented in Table III,

TABLE III.—EFFECT OF INTRODUCING SEMEN PLUS ANTIBIOTICS OR LUGOL'S SOLUTION INTO THE UTERI OF COWS IN THE LUTEAL PHASE

Treatment	No. of cows	No. with pyometra	No. infected on culture
Semen + antibiotics	3	0	0
Semen + *C. pyogenes* + antibiotics	3	3*	0
Lugol's solution	2	2	0

*All slight.

show that in the cows inseminated with semen without added *C. pyogenes*, no pyometritis developed and the uterine swabs at slaughter were sterile. In those inseminated with semen containing added *C. pyogenes* a slight sterile pyometritis was present in each case. Neither semen sample showed any growth on bacteriological culture just prior to insemination.

In many veterinary practices the standard treatment for endometritis and other sterility troubles involves uterine irrigation with Lugol's iodine solution during the luteal phase. We were interested to know whether or not this, in fact, was a desirable practice. Also many gynæcologists take human uterine biopsy samples during the luteal phase to check the degree of glandular proliferation and also carry out curetting at this time. To test the effect of uterine irrigation with Lugol's solution during the luteal phase, a preliminary experiment was carried out on 2 cows which had no previous clinical symptoms of pyometritis. After taking cervical swabs (which proved sterile on culture) 50 ml. Lugol's solution was inserted into the uterus using an inseminating tube and syringe. The animals were killed two days later and both had a severe sterile pyometritis. Although it is probable that most of the infection introduced would clear at the next œstrous period, there is always the possibility that inflammation of the uterine tract might result in permanent damage. In view of our later experience on alternative methods of treating endometritis in cattle we believe that uterine irrigation with Lugol's solution should be viewed with suspicion. Many of our animals which have been repeatedly used as receptor cows and in which the uterus had been entered on several occasions during the luteal phase have become permanently sterile.

Our results on the use of antibiotics in semen strengthen the evidence of their value in routine insemination practice. Many cows are inseminated at the end of heat and even at or near ovulation which occurs in the cow approximately fourteen hours after the end of heat. Since Edgar (1952) has shown by chromatographic techniques that progesterone is present in the bovine follicle before ovulation the question is raised as to whether insemination at this time with infected semen might not produce uterine infection and result in implantation failure. Is the small rise in conception rate (about 5%) concomitant with the addition of antibiotics to semen used in artificial insemination practice due, in fact, to the prevention of uterine infection in the small number of cows inseminated well after heat? Can the published variations in the value of adding antibiotics to semen be attributed to variations in the percentage of cows inseminated late after heat? Also, since many workers have consistently failed to show any effect of antibiotics on the metabolism of sperm, do our results then help to explain why antibiotics have more beneficial effects on the conception rate of bulls of low fertility, since such animals often have higher semen bacterial counts and would be more likely to infect cows inseminated later after heat?

Since ovarian hormones can influence the resistance to uterine infection, we were interested to know if we could successfully treat the condition of pyometritis with hormones.

In the cow, where manual removal of the corpus luteum is possible, one can remove the main source of endogenous progesterone. However, in the human where such a procedure is not possible, it would be of more value if œstrogens could be used to counteract the action of progesterone. Our last two experiments were designed to test our ability to produce and control pyometritis in the cow.

In these experiments, in order to be as uniform as possible, it was decided to use the standard culture of *C. pyogenes* alone as an infective agent and to dispense with the use of semen with its variable bacterial content. 6 cows in the luteal phase were inseminated with a culture of *C. pyogenes* after taking cervical swabs. Two days later the existence of pyometritis was confirmed in each cow by removal of pus from the uterus using a sterile speculum and sterile inseminating syringe and pipette. The pus was then cultured for growth of *C. pyogenes*. On the same day the corpus luteum was expressed manually from the ovary. The cows were then allowed to come on heat naturally (usually two to four days after the removal of the corpus luteum) and were killed two days after heat. As shown in Table IV, in no case was pyometritis present and the bacterial swabs of the uteri at slaughter were sterile. We had thus experimentally produced pyometritis and then removed it. We were interested to know if injections of stilbœstrol would produce the same effects in the presence of a corpus luteum.

Following an identical procedure as in the last experiment of producing a pyometritis and checking its existence, 10 cows were then treated with stilbœstrol at various dose levels. The hormone was injected intramuscularly and the animals killed three days after injection with the results shown in Table IV. Injections of 25 mg. stilbœstrol in 2 cows did not remove pyometritis and the bacterial

TABLE IV.—THE EXPERIMENTAL CONTROL OF PYOMETRITIS

Treatment	No. of cows	No. with pyometra	No. infected on culture
Removed corpus luteum manually	6	0	0
+ 25 mg. stilbœstrol i/m	2	2	2
+ 50 mg. „ „	2	2	2
+ 75 mg. „ „	3	1	3
+ 100 mg. „ „	3	0	0

(i/m = intramuscularly.)

swabs at slaughter were heavily infected. Similarly, 2 cows received 50 mg. stilbœstrol and although this dose level produced a flow of pus through the cervix it did not entirely remove the pyometritis. In 3 cows receiving 75 mg. the uteri of 2 appeared devoid of pus but cultural examinations of the uterine swabs showed that all were, in fact, infected. 3 cows which received a single dose of 100 mg. stilbœstrol had sterile uteri even though a heavily infected pyometritis was present three days previously.

Thus we had been able to show quite clearly that the susceptibility of the uterus to infection is related to the relative levels of progesterone and œstrogen, and that the effect of one may be overcome by an excess of the other. It appeared that this was the most likely reason for failure of transplantation of ova in the cow for it is almost impossible under field conditions to be certain that no bacteria are carried through the cervix during the operation.

This relationship is, however, more important than just indicating why ovum transplantation failed for it may well indicate a relationship of ovarian hormones and the resistance of an animal to disease. It is quite certain that the uterus is highly resistant to certain bacteria during œstrus, but not yet clear whether this is a local or general effect. There are certain indications that the effect is general. von Haam and Rosenfeld (1942*a*, *b*, *c*) showed that antibodies produced in rabbits after injections of pneumococci were at a higher level when œstrone was given than otherwise, and Foley and Aycock (1944) found that a very much lower percentage of mice died after injections of streptococci when stilbœstrol was given than when no stilbœstrol was administered. Moberg (1952) observed that there was a considerable increase in blood leucocyte numbers in cattle during œstrus as compared with blood obtained during the luteal phase. These results suggest that total body resistance may be affected by ovarian hormone levels.

Alternatively, œstrogen does, according to Hansel and Asdell (1951), result in the proliferation of the terminal blood supply to the bovine uterus, and in the rabbit œstrogen is known to increase the blood flow through the uterus. The increased blood flow may strengthen uterine resistance to infection and prevent polymorphonuclear cell accumulation. Œstrogens also stimulate uterine contraction and increase the flow of mucus through the cervix which may also aid the uterus to resist infection. In contrast, is the action of progesterone in increasing the susceptibility to infection due to its effect on the uterine mucosa? Progesterone by increasing glandular activity and the formation of uterine milk may supply not only an essential nutrient for the developing egg but also one most suitable for bacterial growth. If this were so the overriding effect of high doses of œstrogen over progesterone (*see* Table IV) might be due to its effect on the uterine mucosa.

Endometritis appears to be of considerable importance in cattle during winter and often results in delay in conception usually until spring grass becomes available. A persistent corpus luteum in the cow is often accompanied by pyometritis. We think that in some cases the œstrogen level at normal heat periods during the winter is often insufficient to clear established infections, especially as winter heat periods are often short, with a minimum of œstrous behaviour. Nor is the damage removed when the uterus again becomes healthy, for in our extensive records on the use of slaughterhouse dairy cows, we have had many cases of blocked fallopian tubes, probably due to previous endometritis rendering such animals permanently sterile, which, no doubt, is why many of them were sent to slaughter.

Veterinarians have long been interested in the problem of treating bulls for genital infections of trichomoniasis and *Vibrio fœtus* for, once infected, a bull remains infected for life. In the cow, spontaneous recovery from these infections occurs when the animal is allowed several heat periods without reinfective coitus. We feel that this may be due to the recurrent periods of high œstrogen level without an extended period when progesterone predominates. It is known, however, that cows infected with *Vibrio fœtus* may become pregnant and still be infected at calving, which is to be expected, for such animals would have no recurrent periods of high œstrogen level and their hormonal state would be similar to that of the bull. In the bull testosterone is produced continuously, and since testosterone has a systemic effect similar to progesterone in the cow, spontaneous recovery in the bull seems unlikely.

While the extensive use of antibiotics together with improved hospital practice have reduced deaths due to puerperal sepsis, if the findings just described apply to the human, they indicate that the woman after confinement or after criminal abortion is very susceptible to uterine infection, and illustrate why puerperal sepsis was a frequent cause of death. We have no experience on the use of hormones in the human field but suggest that there may be cases of genital infections in the male where œstrogens might prove beneficial.

In spite of our defined results so far, many pressing problems still remain unanswered. Our investigations have been mainly confined to the use of *C. pyogenes* and other bacteria found in bull semen to which the bovine uterus appears resistant during heat. However, infections of *Vibrio fœtus* and trichomoniasis certainly are transmitted at œstrus so it is obvious that there are probably variations in the general scheme about which we need further experimental evidence.

We are continuing studies on rabbits to determine whether this effect is localized to the uterus or applies to total body resistance, and on bulls to determine the effect of periodic injections of stilbœstrol on trichomonad and *Vibrio fœtus* infections. We are interested in obtaining evidence as to whether or not cows with endometritis and pyometritis do conceive shortly after removal of a corpus luteum or after treatment with stilbœstrol.

Finally, we wish to thank Dr. R. M. Fry and Dr. J. M. Boissard of the Public Health Laboratories, Cambridge, for carrying out the bacteriological examinations in these studies.

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Dr. **G. I. M. Swyer** pointed out that there appeared to be far less susceptibility to intra-uterine infection during the luteal phase in women than in bovines. In the investigation of human infertility, it was routine practice to take an endometrial biopsy during the luteal phase; although no elaborate precautions against the introduction of bacteria from the lower reproductive tract were taken, it was exceedingly rare for this minor procedure to be followed by uterine infection. Indeed, the frequency with which conception was encountered in the same cycle as that in which the biopsy had been taken, the pregnancy then proceeding normally, had led to the suggestion that taking an endometrial biopsy might even facilitate nidation, perhaps by enhancing the decidual reaction.

It seemed possible that an explanation for these differences between the two species might be due to the fact that in women the œstrogen level during the luteal phase, far from being lower than during the proliferative, pre-ovular phase, rose to even higher values, corresponding with the peak of progesterone secretion. Perhaps in the cow œstrogen production did not rise in this way during the phase of corpus luteum activity.

Dr. Mavis Gunther said that more than a decade ago she had observed what had appeared to be an increased susceptibility to infection some days after single large doses of œstrogens. Women in three groups had received respectively no treatment, ascorbic acid tablets, or a single dose of 20 mg. stilbœstrol immediately after delivery. 3 women among the 50 in this third group developed puerperal infection with hæmolytic streptococci about seven days after delivery. There were no other cases of infection, and no apparent means of transmission between the 3 cases. They were not concurrent nor in the same rooms. All patients had been allocated to their types of treatment at random at delivery. Although the investigation had been made for other purposes the effect of stilbœstrol on the uterus had been expected to be a reduction in the risk of infection through restoration of the endometrium: indeed a reduced morbidity rate has been observed by Connally *et al.* (1940) among patients receiving stilbœstrol for the suppression of lactation. The interpretation of the 3 infected cases had been that if they were attributable to the treatment, the single large dose had enhanced the post-partum œstrogen withdrawal and had postponed the repair of the endometrium. The contrast in susceptibility to infection before and after ovulation in the cow, described by Mr. Rowson and Dr. Lamming, had been found where there was no denudation of the uterine cavity, and one had to look for some other explanation. One suggestion came to mind. There was some evidence that mucopolysaccharides were concerned in the regulation of bacterial flora. It had seemed to the speaker that since the body depended on its intestinal flora for health it must have some means of encouraging the right bacteria and discouraging pathogens. The transition of flora between the small and large intestine and other considerations had suggested that mucopolysaccharides were concerned in this control. György *et al.* (1952) had shown that polysaccharides related to the ABO blood groups present in human milk acted as growth factors to *Lactobacillus bifidus* and as deterrents to others. Possibly the contrast in susceptibility observed in cows was mediated by mucins secreted under the influence of œstrogens. While the animal was on heat and when, in nature, organisms might be introduced into the reproductive tract the endometrial or cervical mucins might be protective. After ovulation the type of secretion might be modified and the medium in the uterine horns be particularly suited to the growth both of the ovum and bacteria. The effects described by Mr. Rowson and Dr. Lamming might be attributable more to the actions of œstrogens than to those of the corpus luteum.

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Mr. A. E. Pierce: It has been known for some time that *T. fœtus* can colonize the uterus of cattle for protracted periods only in the presence of a persistent corpus luteum, and that spontaneous recovery usually accompanies a return to œstrus. Whereas the reproductive tract of cattle has been shown to develop specific local antibodies against *T. fœtus*, these alone do not appear capable of eliminating the infection. It is not clear, however, whether the suggested hormonal action is directly antimicrobial or indirect, as for example through induced changes in the uterine endometrium. Hormones, however, might also influence the development of local antibodies. Since it is difficult to infect the bovine with *T. fœtus* at any time other than at œstrus it is doubtful whether œstral hormones in this case play any significant part in determining resistance to infection by *Trichomonas fœtus*.

Section of Obstetrics and Gynæcology

President—A. C. PALMER, O.B.E., F.R.C.S., F.R.C.O.G.

[*January* 23, 1953]

THE following Specimens were shown:

Chorio-adenoma Destruens Treated by Hemihysterectomy.—Mr. ALAN BREWS.

Theca-cell Tumour.—Mr. A. F. CLIFT.

Ectopic Carneous Mole in a Lower Segment Cæsarean Scar.—Mr. C. KEITH VARTAN.

Death from Fulminating *B. welchii* Infection following Induction of Labour with a Drew Smythe Catheter.—Mr. N. A. RICHARDS.

Pregnancy in One Horn of a Bicornate Uterus.—Dr. GUY ROWORTH.

Highly Malignant Granulosa-cell Carcinoma of the Ovary.—Dr. ANTHONY PEARSON.

Large Bladder Stone and Bilateral Pyonephrosis Complicating a Repair of Prolapse.—Mr. G. B. LIVINGSTON.

[*February* 27, 1953]

DISCUSSION ON PREGNANCY TOXÆMIA

Dr. R. H. J. Hamlin (New Zealand) (formerly Medical Superintendent, The Women's Hospital, Crown Street, Sydney): *The Prevention of Pre-eclampsia by means of Diet and Weight-control* (Synopsis).

Observation of 18,000 booked patients (all seen personally by the author at some stage of their pregnancies or labours) encouraged him to state that pre-eclampsia can be greatly reduced in its incidence and severity by ante-natal care.

A graph recently published by Dieckmann (1952) was exhibited (Fig. 1). This proved that patients in New York who developed severe pre-eclampsia in late pregnancy began, as early as the 13th week of pregnancy, to gain weight at an abnormal rate. It was demonstrated upon this graph that the normal weight-gain for Dieckmann's patients, from the 20th to 30th weeks of pregnancy, was 7·7 lb. (3·5 kilograms). The following statement by Dieckmann was quoted:

> "More attention must be paid to weight-control before the 20th week. Patients must be told the kind of foods and shown the actual amounts. If necessary, they must be hospitalized for several days for further instruction" (Dieckmann *et al.*, 1952).

Exactly this type of diet instruction and weight-control had been carried out at the Women's Hospital, Crown Street, Sydney, during the four years 1948–1951; this hospital containing 220 obstetric beds and having 4,500 booked confinements annually.

Throughout the twelve years which had preceded this new regime, 106 cases of eclampsia had occurred among 36,700 booked cases in spite of standard ante-natal care intensively applied by experienced obstetricians. This was an average incidence of 1 booked eclampsia in every 350 cases, and was similar to that found in five other teaching hospitals (Hamlin, 1952).

During the twelve months which ended in December 1947, there had been one booked eclampsia every three weeks (17 cases) and 2 of these cases had died. Other cases of eclampsia throughout these twelve years had, in some instances, only been averted by late pregnancy vigilance and by energetic measures exerted when patients were approaching term or were in early labour. Pre-eclampsia, accepted as a necessary evil of obstetrics, was seen in the hospital wards in December 1947 as a formidable disease requiring expert nursing, intensive medical treatment and the free employment of measures designed to induce labour. Consequently a good deal of expensive equipment for the accommodation of small premature babies, born following the induction of labour for pre-eclampsia, was in constant use then. Pre-eclampsia was prevalent and severe and together with eclampsia was responsible for one-third of the maternal deaths occurring in the State of New South Wales.

This being the situation in December 1947, when the eclampsia rate was rising in spite of conscientious ante-natal care, renewed efforts were made. After these efforts had been in progress for six months, it became obvious to the present author that the incidence of eclampsia would not be greatly reduced

by *standard* ante-natal methods. He considered that an attack must be launched against pre-eclampsia in early pregnancy and in mid-pregnancy. The attack, as it developed, followed seven steps which have been described in a previous paper (Hamlin, 1952). The most important weapons in this attack

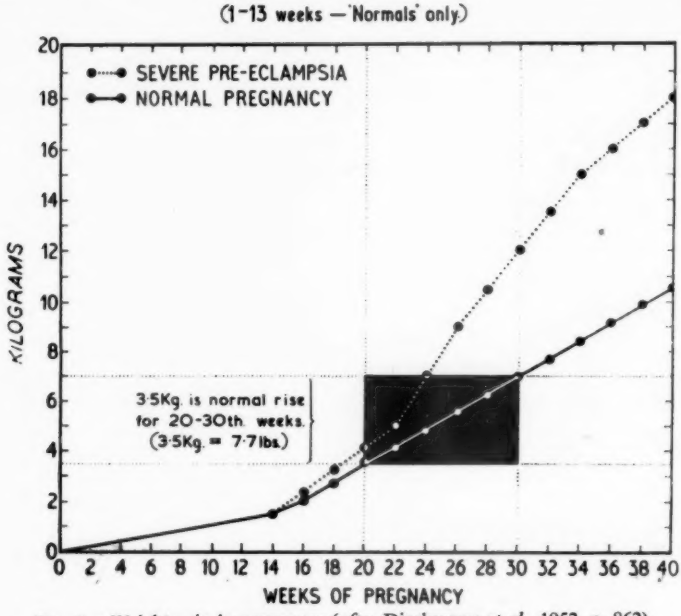

FIG. 1.—Weight-gain in pregnancy (*after* Dieckmann *et al.*, 1952, p. 862).

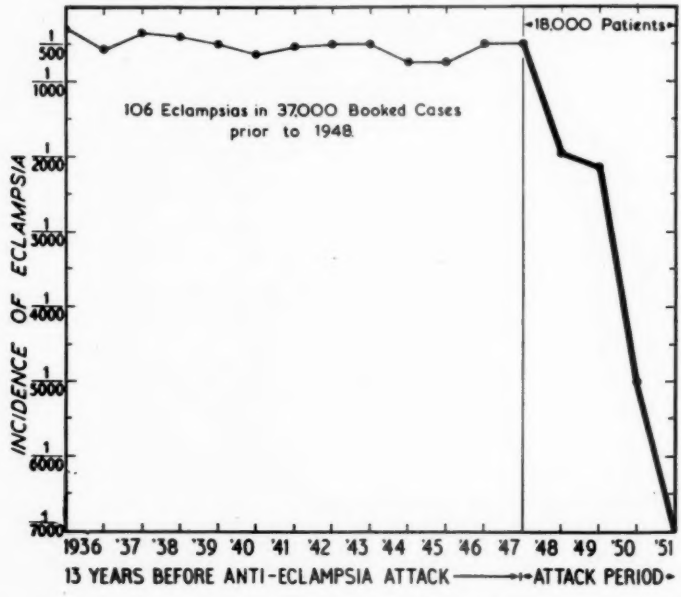

FIG. 2.—Effect of anti-eclampsia campaign, 1948–1951. Women's Hospital, Crown St., Sydney.

were: (1) Diet instruction from earliest pregnancy; (2) Weight-control in early and in mid-pregnancy; (3) The recognition of pre-eclampsia in its pre-hypertensive phase.

The previous paper reported the results obtained up to the month of March 1951, by which time the booked eclampsia rate had been reduced to a low level (1 in 5,000 cases).

The present paper carried that report to the end of the year 1951 and described: (1) The later efforts made in the attack against pre-eclampsia. (2) The fall in the incidence of pre-eclamptic albuminuria from 10% (418 cases) in 1946 to 1·8% (84 cases) in 1951. (3) The further fall in the booked eclampsia rate to 1 in 7,000 deliveries by December 31, 1951 (Fig. 2).

It was stated that the new ante-natal care had so reduced the incidence and severity of pre-eclampsia that, during the final eighteen months of the campaign, induction of labour, between the 30th and 37th weeks of pregnancy, was rarely performed, and Cæsarean section for this indication was not employed at all. Since the disease of pre-eclampsia causes a considerable fœtal mortality, the suppression of pre-eclampsia, it was hoped, would be accompanied by a lowering of the stillbirth and neo-natal death-rates; and this was found to be the case. Thus the combined (corrected) stillbirth and neo-natal death-rate had fallen from 25 per 1,000 live births in 1947 to 11·9 per 1,000 by December 31, 1951. This was a salvage of fœtal life at the rate of 50 babies per annum.

The author referred to Stevenson's series (1952) of 1,600 private obstetric cases treated in Sydney by diet instruction and weight-control throughout pregnancy. Stevenson's pre-eclampsia rate was only 1·06%. After a further study of the hospital records, taken together with Stevenson's report and Dieckmann's paper, the present author re-stated his own second postulate (Hamlin, 1952) of pregnancy toxæmia in the following terms:

> "If any patient, whether primigravid or multigravid, does not increase her weight by more than 8 lb. between the 20th and 30th weeks of pregnancy, *or in any earlier ten-week period*, she will not, in the vast majority of cases, have pre-eclampsia, *either mild or severe*."

APPENDIX

The Diet Used for Normal Pregnancy

		Protein grm.	Fat grm.	CHO grm.	Calories	Thiamine units	Ascorbic acid mg.	Ca mg.	Fe mg.
Breakfast									
Oatmeal	½ cup	3	2	20	106	162	—	15	1·2
Egg	1 egg	6	6	—	80	75	—	30	1·5
Bread	1 oz.	2	—	15	69	61	—	7	0·6
		11	8	35	255	298	—	52	3·3
Lunch	oz.								
Meat	3	14	19	—	240	32	—	8	2·7
Lettuce	½	—	—	—	—	11	—	—	0·1
Tomatoes	4	—	—	2	6	17	20	12	0·4
Raw carrots (grated)	½	—	—	2	6	8	—	6	0·05
Bread	2	3	—	30	137	122	—	14	1·2
Orange	4	—	—	11	40	64	47	34	0·4
		17	19	45	429	254	67	74	4·85
Supper	oz.								
Meat	4	18	26	—	320	72	—	16	3·6
Potato	4	1	—	16	68	104	12	8	0·8
Cabbage	3	—	—	3	10	25	20	16	0·3
Pumpkin	4	—	—	6	27	—	4	10	0·4
Apple	4	—	—	13	48	40	11	4	0·4
		19	26	38	473	241	47	54	5·5
Milk	2 pints	40	44	52	756	466	11	1,400	0·36
Butter	1 oz.	—	23	—	210	—	—	—	—
		87	120	170	2,123	1,259	125	1,580	14·01

Summary

The years 1935–1947 at The Women's Hospital, Sydney, were years when standard ante-natal care, with its emphasis on late pregnancy vigilance, was relied upon. They were not notable for a reduction in the booked eclampsia or pre-eclampsia rates.

They were followed by the years 1948–1951 when late pregnancy vigilance against toxæmia came to be regarded as merely a stop-gap measure to be replaced by:

(1) A dietetic attack, reinforced by weight-control throughout pregnancy.

(2) The search for and treatment of pre-eclampsia in its pre-hypertensive phase.

By such methods the incidence of pre-eclamptic albuminuria was lowered from 10 to 1·8 per cent, the prevalence of extreme prematurity reduced, the stillbirth and neo-natal death-rates halved and the booked eclampsia incidence brought down to a final level of 1 in 7,000 cases (Fig. 2).

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Dr. H. M. Carey (Postgraduate Medical School, Hammersmith Hospital, and Institute of Obstetrics and Gynæcology, University of London): *Ion Exchange Resins in Pre-eclampsia.*

Many of the major hazards of maternal, fœtal and neo-natal life, such as sepsis and hæmorrhage, have been greatly reduced by the introduction of antibiotics, the development of efficient blood transfusion services and improved antenatal care. Attempts to gain the mastery over "toxæmia", however, have not been so successful. During the last ten years it has become resistant to attempts at further reduction of its baneful effects and has continued to baffle the obstetrician by its elusive ætiology, so that its treatment has remained empirical or symptomatic. Each year "toxæmias" are responsible in England and Wales for 80 maternal deaths, 2,600 stillbirths and 1,400 neo-natal deaths, while in the United States these figures are five times greater. Any practical method of controlling this disorder would thus save many lives in addition to reducing the morbidity of pregnancy.

Pre-eclampsia Follows Salt Retention

Dieckmann *et al.* (1950, 1952*a*, *b*) have experimentally accentuated pre-eclamptic signs by the administration of sodium chloride, while Mukherjee and Govan (1950) have demonstrated a correlation between the severity of the œdema and the extracellular sodium concentration. In moderate and severe pre-eclampsia Lloyd *et al.* (1952) claim there is an increase in urinary mineralo-corticosteroid excretion which may be responsible for the sodium retention.

At the Postgraduate Medical School, Hammersmith Hospital, the total body sodium has been determined by a radio-isotope dilution technique twenty-four hours after admission and on the ninth post-partum day. The differences between these two estimations, expressed as a percentage of the post-partum reading, are shown in Table I. They show that even in the early stages of pre-eclampsia

TABLE I

	% Salt Retention*		Weight gain in lb.	
Normal Pregnant	24		22	
	25		N	
	28		N	
	28	Average	19	Average
	28	27	32	25
	29		28	
Mild P.E.T.	32		36	
	33		39	
	39		42	
	48	Average	28	Average
	48	43	35	37
	50		36	
	52		40	
Hypertension and P.E.T. ..	39		28	

* in excess of total body sodium on the 9th day post-partum.
N = weight gain in the latter part of pregnancy was within normal limits. Data on early part of pregnancy were not available.

there is an appreciable retention of sodium which does not correlate with excessive or rapid weight gain. The amorphous component of the suprarenal cortical secretion has twenty times the salt-retaining activity of desoxycorticosterone (Grundy *et al.*, 1952), and it is possible that the secretion of this fraction may be stimulated by the centre which controls the volume of extracellular fluid, or by an ACTH like material which Opsahl and Long (1951) have extracted from the placenta. Hechter *et al.* (1951) have demonstrated the conversion of progesterone to corticosteroids in perfused adrenals so the reduced excretion of pregnanediol in pre-eclampsia may be an indication that more progesterone is being converted to corticosteroids. De Courcy *et al.* (1952) have extracted cortisone, 17-hydroxy-corticosterone and at least three other unsaturated 3-ketosteroids from the human placenta; thus this organ either directly or indirectly may be the source of the hormones responsible for salt retention.

Salt Retention Underlies the Signs of Pre-eclampsia

(1) *Œdema.*—Sodium retention, by slightly increasing the osmotic pressure, stimulates posterior pituitary secretion via the supra-optic nucleus. The antidiuretic principle causes water retention.

(2) *Hypertension.*—Increased suprarenal activity promotes water diuresis and potassium excretion at the same time as sodium retention (Lloyd, 1951; Gaunt, 1952). Sodium retention, without adequate water retention to keep the sodium sufficiently diluted, continues to stimulate the secretion of pitressin. Sodium also increases the sensitivity of the vascular system to nor-adrenalin (Raab *et al.*, 1950) and controls the basal blood pressure (Rosenheim, 1951).

(3) *Albuminuria.*—Rather (1952) has reviewed a large body of evidence which throws doubt on the validity of the classical theory that the glomerular filtrate is normally free of albumin. Protein is filtered by the glomerulus and reabsorbed by the tubule like other high threshold substances. Thus albuminuria is not necessarily evidence of increased glomerular permeability or renal damage. Bull (1948) has shown that a raised venous pressure in healthy young people will produce albuminuria, so that œdema of the renal tissue, enclosed as it is within a capsule, may impede venous outflow and contribute to the production of albuminuria. In animal experiments, suprarenal hormones increase the amount of protein filtered by the glomerulus and decrease the amount reabsorbed by the tubules.

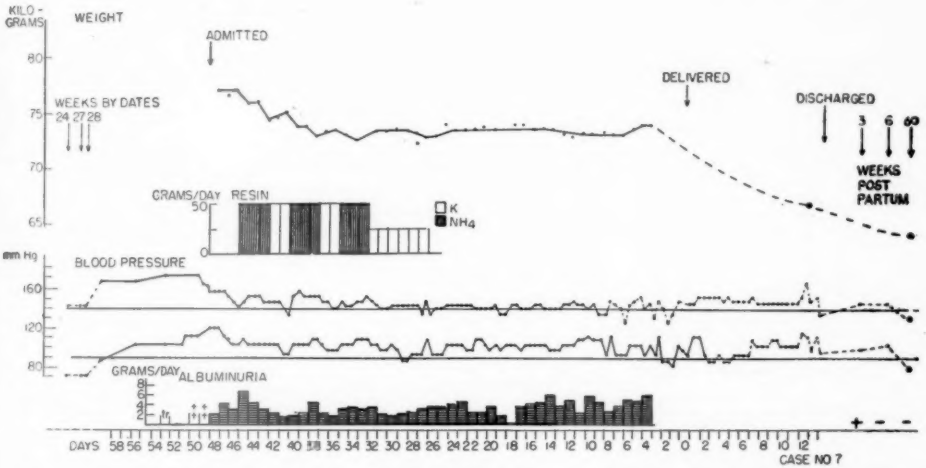

FIG. 1.—Clinical details of a case of pre-eclampsia treated with ion exchange resins. Blood-pressure readings shown are averages of measurements taken every four hours. Albumin content of the urine was determined by the turbidity method. The ammonium resin effectively reduced the weight and œdema, while the blood pressure fell and the albuminuria decreased with administration of the potassium resin. Follow up shows return of blood pressure to normal.

(4) *Fits.*—Hodgkin and Katz (1949) have correlated the initiation of a nerve impulse with an increase in the intracellular sodium and a corresponding loss of potassium. Psychotic manifestations and increased activity in the EEG can be produced by an excess of suprarenal hormones. Macintosh (1952) has drawn attention to the variations in EEG activity and contends that 12% of otherwise normal individuals display cerebral dysrhythmia and are more convulsion-prone than the rest of the population. It is possible that eclamptic convulsions may be precipitated in susceptible women as a result of an elevation of intracellular sodium or a lowering of intracellular potassium.

(5) *Liver pathology.*—Needle biopsy has failed to demonstrate necrosis of liver cells prior to an eclamptic fit (Ingerslev and Teilum, 1945).

Pre-eclampsia is Relieved by Salt Depletion

(1) *Bed rest.*—Most pre-eclamptic patients improve on bed rest. This simple procedure increases renal excretion of sodium even in non-pregnant individuals (Kattus *et al.*, 1949). Bed rest also reduces the venous pressure in the legs and the demands on the circulating blood volume. There is a centre (probably in the hypothalamus) which is concerned with the regulation of the extracellular volume. The compensatory changes which it stimulates occur more slowly than those produced by the osmotic pressure regulating centre in or near the supra-optic nucleus (Black, 1953). By allowing a redistribution of fluid to the head, bed rest will inhibit the sodium retaining influence of this centre.

(2) *Low salt diet.*—Normal diets contain about 10 grammes of salt. This may be reduced slightly by omitting salt from cooking and prohibiting its use at table. On a "salt-free" diet prepared by a dietitian it is not possible to reduce the salt content of the diet below 2 grammes (800 mg. sodium) without rendering it unpalatable. Clinical improvement in pre-eclampsia is frequently proportional to the extent to which the salt intake is reduced.

(3) *Ion exchange resins.*—These can be used to convert a low salt diet (2 grammes) to an almost true salt-free diet. Resins are large insoluble molecules combined with either ammonium or potassium ions. In the alimentary tract, these ions are exchanged for sodium ions. In this way some of the

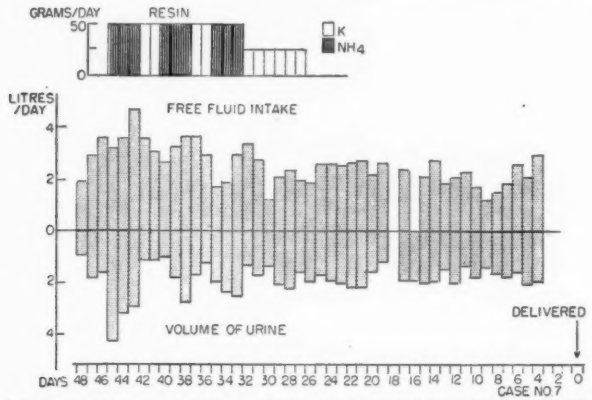

FIG. 2.—Free fluid intake and volume of urine in same case as shown in Fig. 1. The ammonium resin produced a diuresis each time it was given. No restriction was placed on the volume of fluid the patient was allowed to drink.

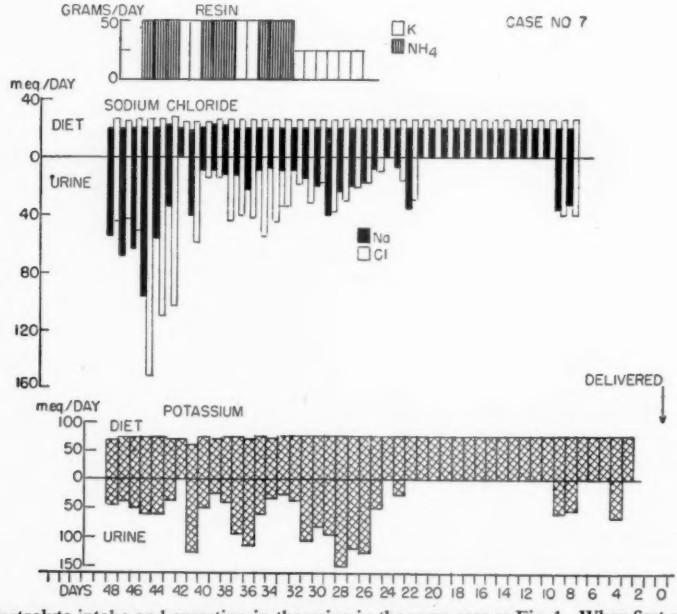

FIG. 3.—Electrolyte intake and excretion in the urine in the same case as Fig. 1. When first administered the ammonium resin increased the urinary excretion of sodium, but this fell off steeply as renal ammonia production got under way. During the maintenance dose of potassium resin the renal sodium excretion increased slowly and then fell off, suggesting replacement and excretion of intracellular sodium. (The weight and sodium intake remained constant during this period.)

sodium is rendered insoluble and its absorption prevented. The ammonium ions, which are liberated in exchange for the sodium ones, are absorbed as ammonium chloride, producing a compensated acidosis, which, in turn, increases the urinary loss of sodium, resulting in a negative sodium balance. The acidosis is effective in promoting urinary excretion of sodium for only two to three days. This is due to the renal ammonium production increasing sufficiently to replace most of the sodium in the urine with the ammonium ion, thus curtailing further sodium loss in the urine.

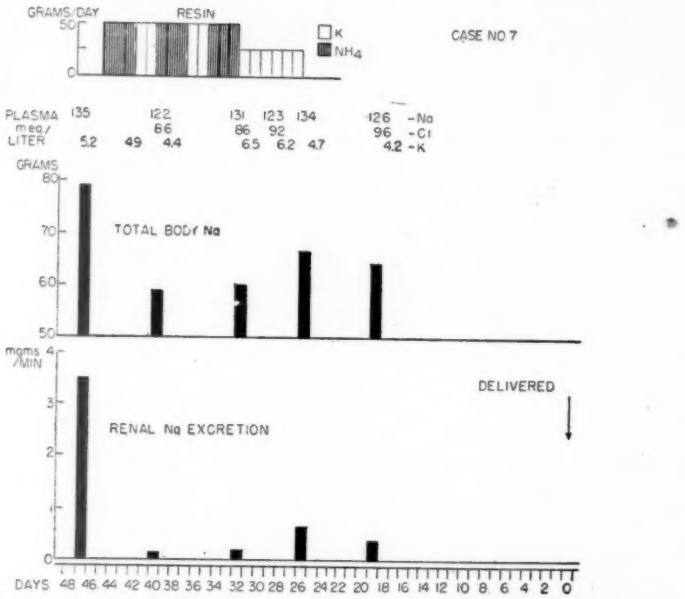

FIG. 4.—Same case as Fig. 1, showing reduction in total body sodium produced by resin therapy. After the first week no further sodium depletion was produced. When resin administration was stopped some sodium retention occurred but more than half of the reduction, which had been produced by the resin, was maintained by the low salt diet. As the body was depleted of sodium, the renal sodium clearance fell to very low levels This acted as a safeguard against excessive sodium depletion.

Clinical Experience with Ion Exchange Resins in Pre-eclampsia

Cases chosen for study were those of moderate to severe pre-eclampsia developing before the 36th week of pregnancy. They had failed to respond to bed rest, low salt diet (2 grammes per day) and sedation.

4 patients to whom resin was administered had developed pre-eclampsia at the 31st, 32nd, 32nd and 35th weeks. They were delivered at the 38th, 36th, 39th and 37th weeks respectively of living infants weighing 6 lb. 8 oz., 5 lb. 14 oz., 5 lb. 1 oz., and 4 lb. 7 oz. Clinical details of two of these cases, both of whom were primiparæ, are shown in Figs. 1–5. The fifth was a case of essential hypertension who developed pre-eclampsia at the 33rd week despite hospitalization from the 29th week. She was delivered at the 36th week of a living infant weighing 4 lb. 8 oz. In 2 cases of pre-eclampsia complicated by hydrops fœtalis, the acute phase was controlled sufficiently to allow induction of labour and vaginal delivery without deterioration in the condition of the patients. The last case in the series was admitted at 36 weeks with excessive weight gain and œdema. Two weeks' hospital treatment on a low salt diet failed to prevent further increase in weight, and at 38 weeks resin therapy was commenced. In all 8 cases, there was a dramatic reduction in weight with disappearance of the œdema and improvement in urinary output. The changes in blood pressure and albuminuria were less marked but showed a satisfactory trend. Dunster, McGowan and Bennett (1953) having been stimulated by earlier reports (Carey, 1952, 1953*a*) treated 7 cases along similar lines and obtained almost identical results. In the light of the author's experience gained with these preliminary trials, the dosage suggested for an average case is 75 grammes of ammonium (carboxylic cation exchange) resin per day for two days then 50 grammes of potassium resin per day for three days, followed by two days' rest. The sequence can then be repeated. After the first or second week, the improvement obtained with the resin can be maintained by a low salt diet (2 grammes per day). Larger doses of resins can be used

with cases giving rise to anxiety, but nausea may develop sooner, and the resin therapy may have to be temporarily discontinued for this reason. During the period of ammonium resin administration, depletion of potassium as well as of sodium occurs. The acidosis produced by this type of resin ceases to be advantageous after the second day, therefore potassium resin is then used to produce a high potassium intake. After ammonium resin administration has been stopped, renal ammonium production will be gradually depressed. When the ammonium resin is again given at the start of the second week, the acidosis it produces will be effective in promoting urinary sodium excretion.

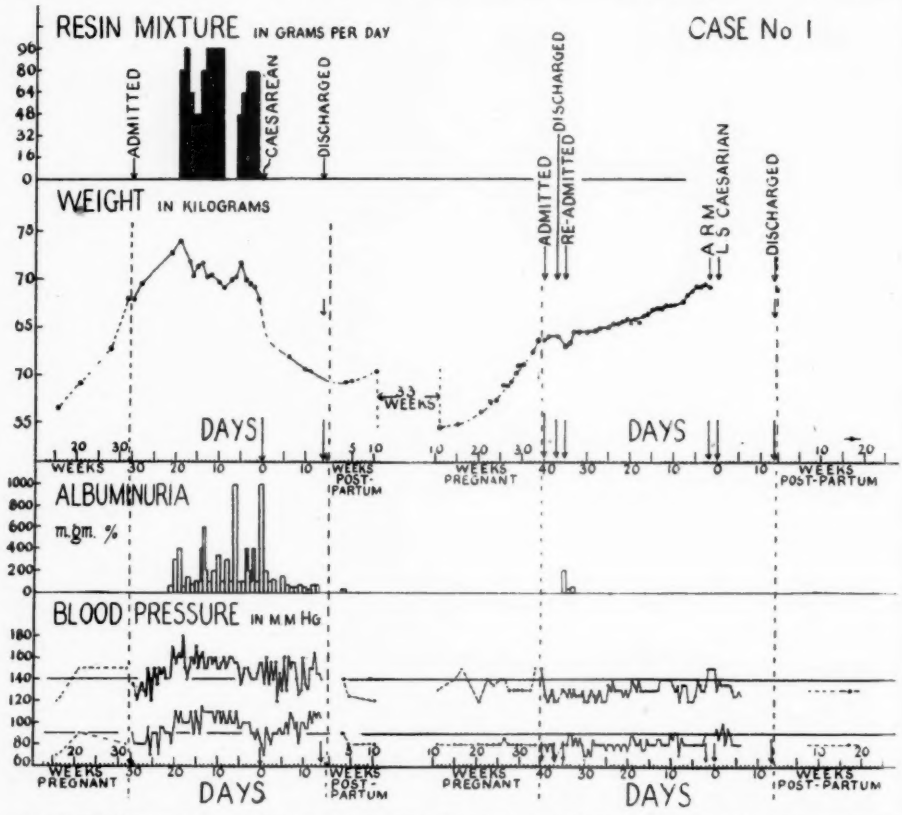

FIG. 5.—Follow-up data on the first case treated with resins. In this case a mixture of half ammonium and half potassium resin was used as it was the only preparation available at that time. During the subsequent pregnancy albuminuria occurred on three days only, and the blood pressure only rose slightly above 140/90 on three occasions. Subsequent experience showed that the Cæsarean section done in this case was unnecessary.

Contributions of Ion Exchange Resins

(1) *Reduction of prematurity and neo-natal mortality.*—Pre-eclampsia is the commonest known cause of prematurity as it is an ætiological factor in 15% of all premature deliveries. By controlling pre-eclampsia with ion exchange resins in conjunction with bed rest and 2 grammes salt diets, these pregnancies can be carried on to 36 or 38 weeks. If fœtal abnormalities are excluded, no case of intra-uterine death has occurred in these cases so far reported. Follow-up studies have failed to show any permanent impairment of the health of the mothers as the result of prolonging their pre-eclamptic pregnancies. This is in agreement with the experience of Dieckmann *et al.* (1952*b*).

(2) *Reduction in the incidence of Cæsarean section.*—In the past, one has often been forced to perform Cæsarean section in cases of fulminating pre-eclampsia lest convulsions occur during the time required for surgical induction and vaginal delivery. As most cases are primigravidæ, subsequent vaginal deliveries, in the presence of a scarred uterus, necessitate close supervision.

By controlling the acute phase of pre-eclampsia with the above therapy, labour can be induced with

greater safety to the mother and sufficient time becomes available for vaginal delivery. This is especially so if labour is induced by the improved technique described elsewhere (Carey, 1953*b*).

Summary

(1) Pre-eclampsia is an endocrinal disorder producing abnormal electrolyte and water metabolism. The "toxin" of toxæmia is excess salt.

(2) Pre-eclampsia is controlled by salt depletion which can be produced by a combination of bed rest, low salt diet and ion exchange resins.

(3) Ion exchange resins convert the salt remaining in a low salt diet into an insoluble form and prevent its absorption. The ammonium resin produces an acidosis which initially increases urinary sodium loss and produces a negative sodium balance. The potassium resin reduces sodium but increases potassium absorption.

(4) By correcting the electrolyte imbalance a pre-eclamptic pregnancy can be prolonged beyond the 36th week thus reducing prematurity and the associated neo-natal mortality without immediate or remote risk to the mother's health.

Acknowledgments

I am indebted to Professor J. C. McClure Browne for constant encouragement in carrying out this work.

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Miss Marjorie Dunster (Bristol): *The Cation Exchange Resins in the Treatment of Toxæmia of Pregnancy.*

The cation exchange resins seemed to me to be one of those things which learned biochemists might understand but which were far above the heads of the hard-working obstetrician and gynæcologist. It was not until I took some time off to visit other centres that I realized the part which the resins might play in the treatment of toxæmia of pregnancy.

Prof. R. J. S. Macdowell has recently shown that there is a definite improvement in cardiac function in cases of cardiac failure treated by reduction in the sodium level with coincident reduction in œdema. In view of this we might reasonably expect to obtain improved renal function and also placental function with corresponding improvement in fœtal oxygenation, in cases of toxæmia of pregnancy. With these thoughts in mind we have treated a series of cases.

Fig. 1 demonstrates the outcome of a typical case in the series.

Each case was treated by a series of short courses of a cation exchange resin containing about 4 parts of ammonium to 1 part of potassium. In order to stabilize the patients prior to the use of the resin they were given complete bed rest and a diet containing 0·8 gramme of sodium. The period of stabilization naturally varied with the clinical condition and as soon as it was judged adequate or the patient's condition showed deterioration a course of the resin was started.

During each course of the resin the graphs showed that in every case there was a marked diuresis and weight loss together with a marked fall in the amount of albuminuria measured in grammes per twenty-four hours. Between the courses there was a tendency to fluid retention with a weight gain,

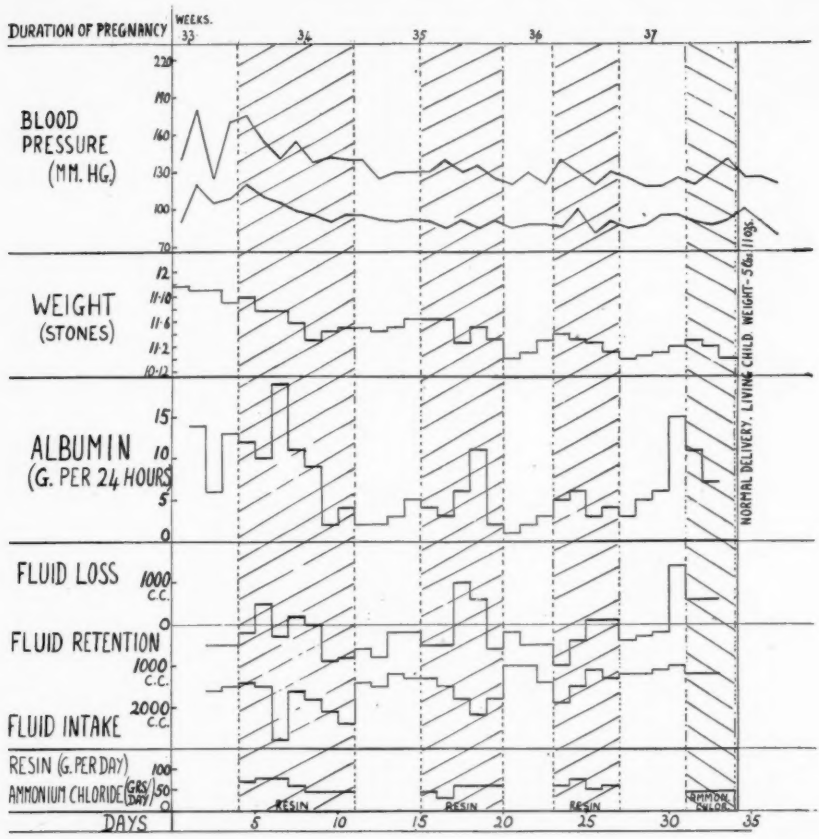

FIG. 1.—Demonstrates the tendency to stabilize the blood pressure at a lower level. It shows the fall in weight and the amount of albumin in the urine during and immediately after each course of the resin, with an increase in both before the next course. Ammonium chloride, although apparently effective in this case, was found on subsequent trial to be of little value.

often of as much as 3–4 lb. in as many days. The albuminuria also tended to rise following the cessation of the resin and to fall rapidly again with its reintroduction. The blood pressure, too, can be seen to show a definite tendency to stabilize at a lower level.

I feel that the improved renal function may be due to reduction of renal œdema with consequent better oxygenation and function.

Mr. Norman Morris (First Assistant in Obstetric Unit, University College Hospital): *Hexamethonium Compounds in the Treatment of Pre-eclampsia and Essential Hypertension in Pregnancy.*

HEXAMETHONIUM (C6) and pentamethonium (C5) are ganglion-blocking agents. They act on the preganglionic synapse and affect both sympathetic and parasympathetic ganglia. One of their main effects therefore is to produce a profound fall in blood pressure. For this reason they have been used recently in the treatment of hypertension and have proved particularly effective during hypertensive crises. Their long-term therapeutic value, however, seems more doubtful.

Apart from a report by Mulcahy (1952) of 10 cases there has been no serious attempt to determine the value or dangers of this form of treatment in pre-eclampsia or essential hypertension in pregnancy. This paper analyses a combined series of 26 cases in which hexamethonium therapy was used. These were not all under my care but also include cases treated by Mr. Leslie Williams and Mr. J. G.

Dumoulin, to whom I am very much indebted for their generous co-operation. Mr. J. V. O'Sullivan and Dr. A. S. Duncan have also kindly sent me details of 2 further cases.

In selecting cases suitable for this treatment we were most careful to choose only those with marked hypertension (180/100 or above) which were not responding to the usual in-patient therapy and where, in addition, if the pregnancy had been terminated a very premature infant with a doubtful prognosis would have been delivered. By lowering the blood pressure we hoped to allow these cases to continue with safety to the mother and thereby to provide an increased prospect of fœtal survival.

Oral, subcutaneous and intramuscular therapy was used following a test dose of 25–50 mg. subcutaneously or intravenously with the patient sitting up in bed. The response to this test dose varied considerably. In some cases it was quite dramatic, whilst in one case there was no response even though the dose was ultimately increased to 250 mg.

The test dose response in 32 cases is indicated in Table I. Not all of these were subsequently treated. A good response was one where the B.P. fell to 120/80 or below. Fair indicates moderate, and poor little or no response.

TABLE I.—RESPONSE TO TEST DOSES OF HEXAMETHONIUM

	Number of cases	Good	Fair	Poor
Essential hypertension	11	9	1	1
Essential hypertension + albuminuria	4	0	2	2
Pre-eclampsia { Hypertension only	4	1	1	2
Pre-eclampsia { Hypertension, albuminuria and œdema	10	2	6	2
Eclampsia	1	0	0	1
Chronic nephritis	2	0	1	1
	32	12	11	9

In severe cases of essential hypertension which had deteriorated 9 out of 11 cases gave a good response whilst in pre-eclampsia unassociated with previous hypertension, a good response was obtained in only 3 out of 14. This suggests that the mechanism of the hypertension differs in the 2 conditions and in pre-eclampsia is sustained by a humoral rather than a nervous factor.

Where oral treatment was used the average starting dose was 250 mg. every eight hours. This was steadily increased until a satisfactory fall was obtained. The degree of response was variable and differed from time to time and day to day. Resistance occurred very soon and the dose had to be steadily increased until daily doses between 3–7 grammes were used.

It is well known that in non-pregnant patients the daily dosage required varies considerably and is probably related to variations in the rate of absorption. In pregnancy absorption may be even more variable. Persistent hypotension and paralytic ileus have yet to be recorded in pregnancy but there seems an equal possibility that they may occur. For this reason I am not entirely in favour of oral therapy although it was used with some effect in 10 cases of this series.

Where subcutaneous or intramuscular treatment was used the initial effective dose varied between 50–100 mg. The maximum effect occurred after twenty-five to forty minutes. Thereafter the blood pressure steadily rose again reaching its previous level in three to six hours. Hourly blood-pressure recordings were taken by day and two-hourly by night. Injections were given every three to six hours providing the blood pressure was 140/90 or more. This avoided periods of hypotension.

Fig. 1 demonstrates what can be described as a fair response. The variation in the fall of blood pressure with each injection is well illustrated as also is the relatively rapid onset of resistance. Fig. 2 shows the same case a few days later responding to an increased dose of 250 mg. every three to four hours. Here again there is considerable variation in response.

It was interesting that even where resistance developed the pupillary dilatation persisted suggesting that the hypertension was now being sustained by increased humoral pressor activity.

Table II analyses the fœtal survival in relation to the method of treatment. It is seen that a relatively higher fœtal survival, 6 out of 10, was obtained with oral therapy compared with 5 out of 14 with

TABLE II

Treatment	Number of cases	Fœtus		
		Alive	Stillborn	Neo-natal death
Subcutaneous or Intramuscular	14	5	4	5
Oral	10	6	2	2
Combined	2	1	1	0

subcutaneous or intramuscular therapy. This observation may be misleading since on the whole the more severe cases were treated by injection therapy. On the other hand the more gradual falls in blood pressure which are obtained by oral therapy may perhaps be more beneficial.

Whilst it was possible to lower the blood pressure in most cases it is very debatable whether this materially altered the course of the disease. In some cases treatment could not be continued for very

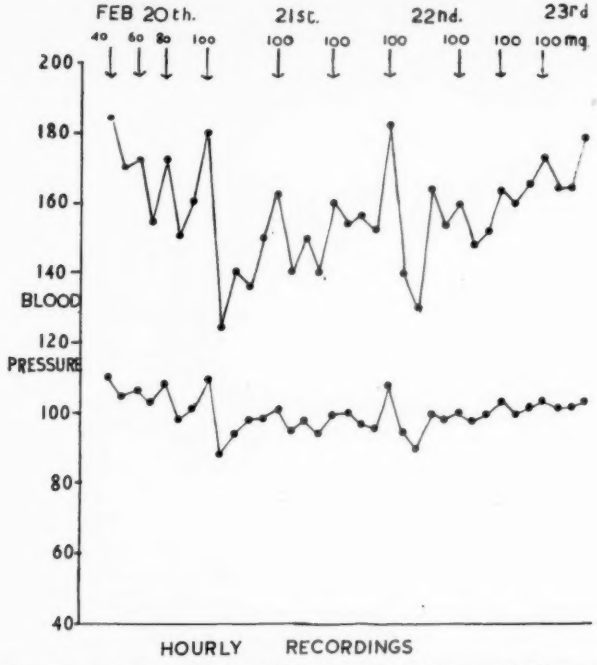

FIG. 1.—Blood-pressure chart showing initial response to intramuscular hexamethonium bromide every three to four hours.

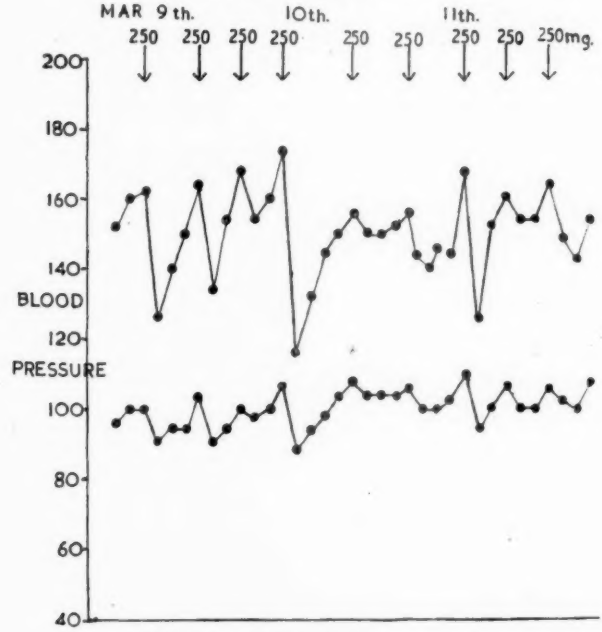

FIG. 2.—The same case fourteen days later indicating a variable response to an increased dose of hexamethonium bromide.

long due to either a poor response, intra-uterine fœtal death or premature onset of labour. In others the initial satisfactory response could not be maintained. No mothers developed eclampsia, accidental hæmorrhage or gross renal damage. If albuminuria was present it usually persisted but did not increase in amount. Œdema seemed to be little affected. All we can claim, therefore, is that in some cases we did appear to stabilize the maternal condition.

Table III analyses fœtal survival in relation to the maturity of the pregnancy when treatment was started and the response obtained. This is a disappointing table since in the very group where we had

TABLE III.—HEXAMETHONIUM THERAPY

Maturity of pregnancy in weeks at start of treatment	Number of cases	Response to treatment			Fœtus		
		Good	Fair	Poor	Alive	Stillborn	Neo-natal death
24–28	4	1	1	2	1	3	0
28–30	4	1	2	1	0	3	1
30–32	5	2	2	1	1	0	4
32–34	9	4	4	1	7	0	2
34–36	4	2	1	1	3	1	0
Total	26	10	10	6	12	7	7

hoped to increase the fœtal salvage rate, namely, in those cases between 24 and 32 weeks, in 13 cases only 2 infants survived. From 32–36 weeks better results were obtained, which was to be expected.

Fig. 3 analyses fœtal survival in relation to duration of treatment. It can be seen that there was a higher mortality in those under treatment for a short period. In 10 cases treatment could only be continued for one to five days. This was related, as stated previously, to either a poor response, intra-uterine fœtal death or premature onset of labour. It is possible that this group includes many where treatment was commenced too late, after extensive placental damage had occurred. Only 3 infants survived.

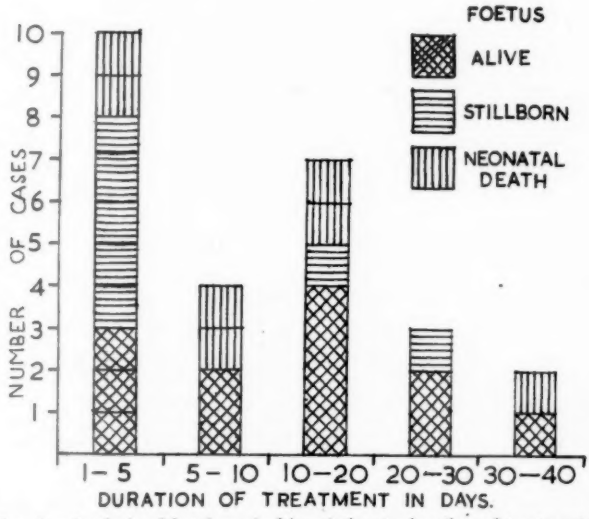

FIG. 3.—Analysis of fœtal survival in relation to duration of treatment.

There was no evidence that continuation of treatment increased fœtal mortality but on the other hand it was not significantly reduced.

Where treatment was continued until delivery no effect upon the normal course of labour was observed.

The maternal side-effects were also not significant. Blurring of vision occurred in nearly every case but the patient soon became adjusted to this. Constipation was also rarely very serious and was easily overcome by the usual measures. Two patients developed a marked skin sensitivity to the bromide but this disappeared when the drug was changed to the bitartrate.

The possible effects of C6 upon the fœtus may now be considered. Maureen Young (1952) has shown in dogs that hexamethonium passes freely across the placental barrier and can very soon be detected in the liquor. If a constant plasma level of hexamethonium is maintained, the C6 content in the liquor

progressively increases until very soon it is well above that in the blood. It then persists in the liquor for some considerable period after the last injection has been given. With these facts in mind we did some hexamethonium determinations on a few patients and the findings are shown in Table IV.

TABLE IV.—HEXAMETHONIUM ESTIMATIONS

		Hexamethonium content
1. Oral treatment until delivery	Cord blood:	9·3 μg./ml.
2. Oral treatment until delivery	Amniotic fluid:	11·0 μg./ml.
	Maternal blood: (at delivery)	3·6 μg./ml.
	Cord blood:	1·0 μg./ml.
3. Last injection 15 hr. before delivery	Maternal and cord blood:	Nil
4. Last injection 20 hr. before delivery	Maternal blood:	a trace
	Cord blood:	Nil
	Amniotic fluid:	5·7 μg./ml.
	Colostrum:	Nil
5. After 2 days' treatment with 20 mg. every 8 hr.:	Amniotic fluid:	0·5 μg./ml.
After 8 days' treatment with 20 mg. every 8 hr.:	Amniotic fluid:	0·5 μg./ml.
72 hr. after stopping treatment:	Amniotic fluid:	4·0 μg./ml.
7 days after stopping treatment:	Amniotic fluid:	Nil

It can be seen that our observations tend to support the previous findings in animals.

We may well ask, does this passage of C6 across into the fœtus and accumulation in the liquor exert any ill-effect?

Post-mortem examination of stillborn infants did not produce any significant findings. In relation to the neo-natal deaths our findings were more interesting. These are shown in Table V.

TABLE V.—NEO-NATAL DEATHS

	Weight	Died after	Post mortem
(*a*)	5 lb. 3 oz.	3 days	Widespread purulent bronchopneumonia
(*b*)	3 lb. 12 oz.	6 days	Gross intestinal dilatation for which transverse colostomy had been performed
(*c*)	5 lb. 14 oz.	8 days	Gross intestinal dilatation with generalized peritonitis
(*d*)	6 lb.	4 days	Cerebral hæmorrhage. Tentorial tear. Atelectasis
(*e*)	2 lb.	4 hours	Prematurity. Atelectasis
(*f*)	3 lb. 5 oz.	8 hours	Prematurity. Atelectasis
(*g*)	3 lb. 7 oz.	68 hours	Generalized pallor. Cerebral œdema. Atelectasis. Histology showed hyaline membrane

Case (*a*) was a healthy vigorous infant at delivery by elective Cæsarean section in spite of aspirating some liquor. It rapidly succumbed to a widespread pneumonia—an uncommon infection in our premature infants.

Cases (*b*) and (*c*) were even more significant. Whilst neo-natal peritonitis is not unknown it is surely more than a coincidence that 2 out of 19 infants born alive demonstrated this marked intestinal dilatation and in yet a third, which survived, there was delay in the passage of meconium.

The other cases show findings more in keeping with those that we expect in premature infants.

It seems possible that the fœtus by constantly absorbing C6 from the liquor which it swallows may be born with a predisposition to paralytic ileus analogous to that which occurs in adults. It is unlikely that this occurs in every case but only in susceptible infants.

Furthermore, it also seems possible that if liquor is aspirated into the lungs the hexamethonium may inhibit normal bronchial secretion to predispose to pulmonary infection or even atelectasis.

Further evidence on these various points is required, however, and other reactions in the fœtus may come to light.

In conclusion, it must be admitted that, on the whole, the results of our treatment were disappointing. Perhaps they would have been better if a more constant control of the blood pressure could have been achieved avoiding the considerable fluctuations which did occur.

I wish to thank Miss Maureen Young who carried out the hexamethonium estimations, and Professor W. C. W. Nixon and Professor McClure Browne for their encouragement and advice in the preparation of this report.

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